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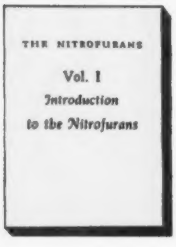

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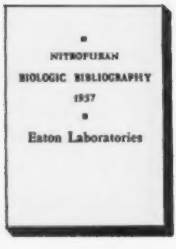

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FOREWORD

Papers included in this issue of *The Yale Journal of Biology and Medicine* were among those presented at a Symposium on "Perspectives in Epidemiology," held at the Yale University School of Medicine on February 20, 1959, the day prior to "Alumni Day." This Symposium, sponsored by the Section of Epidemiology and Preventive Medicine and the Department of Public Health, was a demonstration of the new kinds of activities which today come under the heading of epidemiology. This so-called "new epidemiology" is no longer a subject limited to the concept of infectious disease. All kinds of disease, disability, and even accidents now have their epidemiologies, including cancer, peptic ulcer, and congenital and developmental defects. The Symposium also called attention to the fact that the "new epidemiology" is no longer a discipline which lies wholly within the framework of schools of public health or departments or ministries of public health, but that it is becoming a broad clinical subject to which the physician has much to contribute, and from which he has much to learn. This development has come about in part from a growing appreciation of the fact that epidemiology represents a scientific basis for the practice of preventive medicine, in much the same way as pathology is basic to the practice of internal medicine and surgery, and, in part, from a new awareness that in this science there are previously unrecognized opportunities to explore the etiology of diseases whose pathogenesis is obscure. Thus the epidemiological approach may prove to be as hopeful a method of unravelling some of the obscurities regarding the cause of such diseases as coronary occlusion, rheumatoid arthritis, peptic ulcer, and multiple scleroris as are the more orthodox histological, biochemical, and microbiological forms of approach. We now see cardiologists, neuropsychiatrists, and even rheumatologists enlisting the epidemiological method to an increasing degree. Such clinicians and specialists may not be aware of this fact but they are actually utilizing the epidemiological approach when they begin to measure and analyze the *circumstances* under which a given disease occurs. Such circumstances may concern the age of the patients, their habits and ways of life, and where they live; they may be of microbiological, nutritional, sociological, or genetic nature, but the basic aim is to find out how these circumstances are instrumental as causes. By such means the role of tobacco smoking in the pathogenesis of lung cancer was unearthed, and the relationship of German measles in pregnant women to the occurrence of congenital defects in the foetus was demonstrated. There are many other examples of this kind.

At this Symposium the following titles and their respective authors were listed:

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Surveillance: New Application of Old Principles in the Control of Epidemics on a National Scale	Dr. A. D. Langmuir, Communicable Disease Center, Public Health Service, Atlanta, Georgia
Discussion	Dr. T. D. Dublin, National Institutes of Health, Bethesda, Maryland
Studies on the Ecology of Arbor Viruses	Dr. R. M. Taylor, Yale University School of Medicine
Serological Epidemiology in Measles	Dr. F. L. Black, Yale University School of Medicine
Vaccination with Attenuated Poliovirus	Dr. Dorothy M. Horstmann, Dr. J. C. Niederman, J. T. Riordan, and Dr. J. R. Paul, Yale University School of Medicine
Asian Influenza in New Haven, 1957-58	Dr. R. H. Green, Yale University School of Medicine
Strain Pathogenicity of Staphylococci	Dr. F. R. Fekety, Yale Medical Center
Global Epidemiology Today	Dr. A. M.-M. Payne World Health Organization, Geneva, Switzerland
Discussion	Dr. J. E. Smadel, National Institutes of Health, Bethesda, Maryland
Epidemiological Aspects of Cancer of the Uterine Cervix	Dr. A. G. Gilliam, National Cancer Institute, Bethesda, Maryland

ABO Blood Groups and Cancer of the Stomach	Dr. C. White and Dr. H. Eisenberg Yale University School of Medicine and Connecticut State Department of Health
Social and Cultural Factors in the Epidemiology of Mental Illnesses	Dr. A. DeB. Hollingshead, Department of Sociology, Yale University
Studies on the Epidemiology of Peptic Ulcer	Dr. J. C. Niederman and Dr. H. M. Spiro, Yale University School of Medicine
Epidemiology of Congenital Defects	Dr. T. H. Ingalls, University of Pennsylvania, Philadelphia, Pennsylvania

The Committee in charge of this Symposium has selected some of these communications for publication in this issue of the Journal. It counts itself fortunate in having been given the opportunity to do so.

JOHN R. PAUL

A. M.-M. PAYNE*

World Health Organization, Geneva, Switzerland

GLOBAL EPIDEMIOLOGY TODAY

In presenting some thoughts on perspectives in global epidemiology, I want to emphasize that we are dealing with a moving picture that changes not only from place to place, but also in time over the centuries, year by year, and even day by day. Imagine the evolution of the world, speeded up so that years pass in seconds, and centuries in minutes. Far back in history there were small foci of human activity about which we know little. Gradually these foci extended and in certain areas there were sudden increases which were the early great civilizations. Imagine the thriving, bustling life in these early cities, confident in the future, when suddenly something happened and it disappeared. In the time scale we are imagining, in a few seconds or a minute or so there is nothing left except stones and bones for archeologists. What happened? In most instances we do not know precisely. Sometimes it was doubtless the depredations of neighboring groups, more virile and aggressive, but without the knowledge or intellectual capacity to maintain and continue the development of the civilization they had conquered.

Sometimes the civilization destroyed or damaged itself unwittingly by its interference with the ecological situation in which it existed. Irrigate and build reservoirs, and you build breeding places for mosquitoes. Malaria may destroy a civilization, as is believed to have happened in Ceylon. Build houses with cellars and unprotected grain stores—domestic rodents will increase, and plague and typhus will follow. Ship negro slaves across the Atlantic for profit—their viruses travel with them, and the planters purchase Yellow Jack as well as labor. Medical historians can certainly provide many other examples of the results of man's ignorance. And ignorance is, in the long run, more dangerous than aggression.

The examples I have given are well known, and we do our best to avoid such risks. But what of the unknown or unrecognized dangers we are facing now? The changes in man's ecology which have taken place in the last century have been greater than the previous changes in the whole of man's known history. I use the word changes rather than the word progress deliberately. Only the future will show whether we have made progress or whether we are building something that may eventually destroy us. I believe

* Chief Medical Officer, Virus Diseases.

that this is no exaggeration, and I am not speaking only of the dangers of nuclear explosions and radiation hazards. Dr. John R. Paul,[8] at the Third International Poliomyelitis Conference, pointed out that our technical skill may have outstripped our ability to apply it intelligently. For example, improved hygiene and sanitation which has rid the major part of the more highly developed parts of the world of typhoid and cholera has been at least partly responsible for the great increase in poliomyelitis.

Man and man-made changes in the environment are only part of the total ecological picture. Vectors and infectious agents are also evolving and undergoing both spontaneous changes due to mutation and natural selection and changes in behavior or structure due to the pressure of the environment. Most of these changes cannot be foreseen, nor can they be prevented. But they must be watched for constantly and investigated promptly in a search for a remedy.

A recent and grave example of this came to light during the World Health Organization's (WHO's) Malaria Control Program, when certain mosquitoes developed resistance to insecticides, due apparently to some genetic change not yet understood. This makes eradication of the disease urgent while we still have insecticides to which the vectors are susceptible. Of course, the search for new and more effective insecticides continues, but we do not known how long the chemists will succeed in keeping ahead of the natural defenses of the vectors.

The evolution of infectious agents may be illustrated by considering the influenza A virus, which seems to be one of the most unstable viruses in certain respects, with the result that we have been able to observe several changes in the short period since we learned how to study it.

Modern influenza may be said to have begun in 1889. Epidemics believed to have been due to influenza have been described at intervals for centuries, but in the latter part of the nineteenth century the incidence, in Europe at least, fell to very low figures: the disease almost disappeared in the 1880's until suddenly in 1889, apparently in Asia, an epidemic began which spread throughout the world in successive waves during the following years. The position before 1889 has never been regained. Although the first influenza virus, the swine virus, was discovered by Shope[14] only in 1929, and the first human strain by Wilson Smith, Andrewes, and Laidlaw[15] in 1933, we have, through serological studies, some evidence of what happened before. The studies of Davenport *et al.*[2,3] provided evidence that a virus related to the swine virus had been present in man about the time of the 1918 pandemic and that the known groups of influenza A virus infected man over more or less well-defined periods, after which they disappeared, apparently completely, in a short time. Early in the 1957 pandemic Mulder,[9] confirmed by

others, showed that certain persons who had lived through the period of the 1889 pandemic had antibodies to the new Asian virus, suggesting that a member of the same group of viruses might have been responsible. Furthermore, these persons usually had a higher level of antibody to the Asian virus than to more recent strains and reacted to the stimulus of vaccine in a way which suggests that their primary stimulus, or "original antigenic sin" as Davenport[8] put it, was indeed with that virus, or a closely related one. I shall return later to the puzzling question as to where this virus might have persisted.

It seems that in the last 70 years there have been at least five major antigenic shifts in the influenza A virus. In 1889 a virus apparently related to the Asian virus appeared, in 1918 the swine virus, in 1934 or thereabouts the prototype human A strain PR8 (I omit WS since this is now considered to belong to the PR8 group although it is somewhat apart), in 1946-47 the FM1 or A1 group appeared and the A group vanished, and most recently but certainly not finally, in 1957 the Asian or A2 group appeared, and it looks very much as if the A1 group has disappeared.

In addition to these major shifts in which it is difficult to show any relationship between the different groups by the hemagglutination-inhibition (HI) test, there have also been many lesser antigenic changes suggesting a continuous evolution of the virus under pressure of the antibody spectrum of the human population, changes doubtless facilitating the survival of the virus and its ability to cause epidemics in man. These changes have been studied during the last 10 years under the WHO Influenza Program,[10] which is a good example of the way the quarrelsome human race can at times forget its differences and co-operate in a concerted investigation of a world-wide problem, which by reason of its nature can only be investigated in this way.

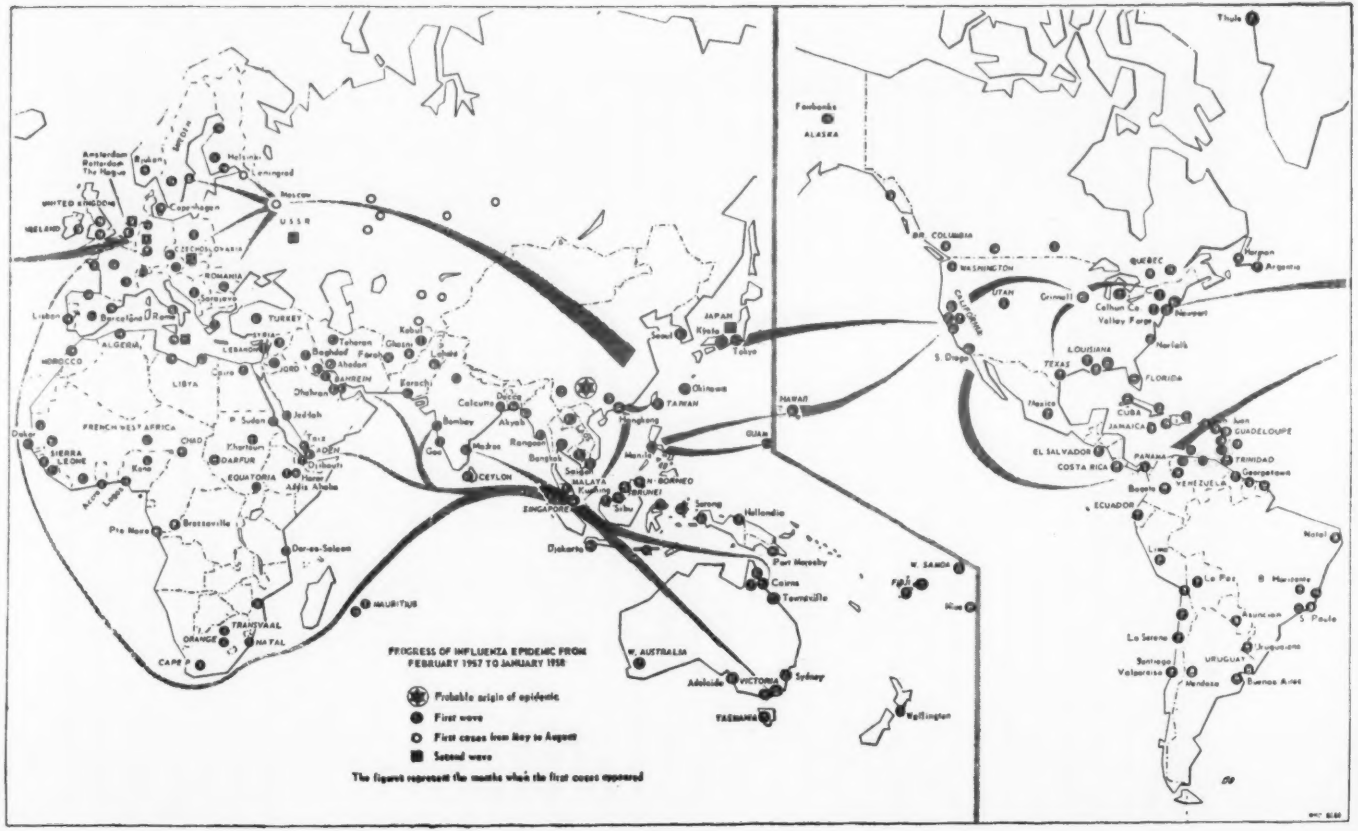
Apart from their scientific interest these changes are of practical importance in the selection of strains for incorporation in vaccines. True, the change from one epidemic to the next may not be sufficient to make vaccines prepared with the previous strain ineffective, but in the course of a few years the progressive change becomes so great that a recent strain must be incorporated in the vaccine. The periodic major antigenic shifts of course demand the inclusion of the new variant. Thus it is necessary to keep a continuous watch on the antigenic make-up of the influenza virus and that is the major function of the WHO Influenza Program. We must also watch for changes in virulence. That is much more difficult to measure, but happily so far whatever it was that happened in 1918 has not recurred.

Another part of the program is the study of the spread of influenza. It seems that there are two principal methods, one being the appearance of a

new variant in one place, followed by continuous spread from there. This was observed in 1949 when a virus recognizably different from previous strains originated in Sardinia and spread northward through Europe.[1] The same was observed even more impressively in 1957,[18] when the Asian virus appeared in South China and spread throughout the world (Fig. 1). The other method of spread seems to depend on the fact that in the intervals between the great pandemics influenza may behave as an endemic disease which periodically takes on an epidemic form. Sometimes new variants of the same group appear almost simultaneously in widely separated parts of the world, causing more or less extensive outbreaks. It would seem that when the immunity status of different populations is similar, the resulting selective pressure on virus mutation and the direction of successful mutation, are also similar so that the same new variant may appear independently in widely separated areas.

However, the appearance of the Asian virus cannot be explained in this way. I have already mentioned its possible relationship to the 1889 virus and that raises the question as to whether this virus has, in fact, persisted since 1889, and if so, where. It is noteworthy that the pandemics of 1889 and possibly also those of 1830 and 1782 appear to have begun in China. There is a possibility that influenza virus may have persisted in an animal host. We know that viruses belonging to the A group naturally infect swine, horses, ducks, and fowls, in addition to man. The swine virus was apparently once a human virus which has persisted with very little change in antigenic structure for 40 years in swine. The absence of antigenic change in this usually unstable virus may be due to the absence of the selective pressure of pre-existing antibody in the pig population, which is regularly replaced by slaughtering and rearing fresh nonimmunes. Perhaps the Asian virus persisted, similarly unchanged, in swine or some other animal host. Some of the properties of the virus, including its susceptibility to nonspecific inhibitors in various animal sera and the capacity to produce hemagglutination with cells of species not normally agglutinated by viruses of human origin lend support to this hypothesis.

During the recent pandemic Dr. Kaplan and I[8] at WHO initiated a study of this problem by arranging the collection of sera from animals (swine and horses) in 25 countries before the pandemic arrived, followed by collection of sera from, as far as possible, the same animals after the human wave had passed. The results suggest that the Asian virus was not present in these animals before, but caused infection in some of them during the pandemic. Time does not permit detailed discussion, but the importance of further investigations is evident. It would appear that these should be carried out also at the point of origin of the pandemic and include studies of both the


PROGRESS OF INFLUENZA EPIDEMIC FROM
FEBRUARY 1957 TO JANUARY 1958
Probable origin of epidemic
First wave
First cases from May to August
Second wave
The figures represent the months when the first cases appeared
Thule
Fairbanks
ALASKA
BR. COLUMBIA
WASHINGTON
UTAH
QUEBEC
Harpon
Argentia
Grinnell
Calhun Co
Valley Forge
Newport
Norfolk
LOUISIANA
TEXAS
FLORIDA
CUBA
JAMAICA
EL SALVADOR
COSTA RICA
PANAMA
VENEZUELA
GUADELOUPE
TRINIDAD
Georgetown
Bogota
ECUADOR
Natal
Lima
La Paz
B. Horizonte
S. Paulo
Asuncion
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Valparaiso
Mendoza
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S. Diego
HAWAII
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JAPAN
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Seoul
Tokyo
Okinawa
TAIWAN
Hongkong
Manila
N. BORNEO
BRUNEI
Sarawak
Hollandia
Port Moresby
Cairns
Townsville
W. SAMOA
FIJI
Niue
Wellington
W. AUSTRALIA
Adelaide
VICTORIA
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Ruhr
Helsinki
Leningrad
Copenhagen
UNITED KINGDOM
IRELAND
CZECHOSLOVAKIA
ROMANIA
Sarajevo
Lisbon
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Rome
TURKEY
SYRIA
LEBANON
ALGERIA
MOROCCO
LIBYA
Cairo
JORD
Baghdad
Ahadan
BAHREIN
Teheran
Farah
Kabul
Ghazni
Lahore
Karachi
Dhahran
Jeddah
P. Sudan
Khartoum
Dakar
SIERRA LEONE
Kano
CHAD
DARFUR
EQUATORIA
Addis Ababa
Dire Dawa
ADEN
Djibouti
Harar
FRENCH WEST AFRICA
Accra
Lagos
Pte Noire
Brazzaville
Dar-es-Salaam
FRANSVAAL
ORANGE
NATAL
CAPE P.
Bombay
Goa
Madras
Calcutta
Dacca
Akyab
Rangoon
Bangkok
Saigon
MALAYA
Kuching
SINGAPORE
Sabu
CEYLON
Djakarta

FIG. 1 .

domestic and wild animal populations there. Unfortunately, China is the one part of the world which the WHO network cannot at present reach. Efforts have been made to stimulate this investigation and are continuing, but so far without success. I mention this to emphasize once more the importance of truly worldwide study of disease problems common to the whole world.

It will be clear that the central theme of these remarks is the importance of studying changes in man, in his environment, and in infective agents and their possible influence on disease patterns. Different parts of the world are changing at different rates—in some areas conditions seem to be much as they were several thousand years ago, in others, conditions exist which have never before been seen on earth. If, therefore, we undertake comparative studies of the existing disease patterns in populations in different areas and in different stages of development, we may obtain evidence as to the influence of past environmental changes on diseases and indications as to the trends which may be anticipated in the future. This is what we need to know to avoid those unknown pitfalls which may lie before us, and also to help newly developing countries from making the same mistakes which we have made.

The best example of this is poliomyelitis since, thanks largely to the pioneer work of Dr. Paul and his colleagues[7] at Yale, we can see actually happening in different parts of the world today the same pattern of evolution of the disease as was experienced in this country over the past century. Furthermore, it is a pattern that may well be followed by other virus infections of similar epidemiology. Indeed, there are indications that this has already begun, in the recognition of epidemic aseptic meningitis and other diseases due to Coxsackie and ECHO viruses, and, perhaps more serious, the grave form of encephalomyocarditis neonatorum described by Gear.[4] It seems probable that the latter only occurs in infants without the protection of maternal antibody. As more women reach maturity without experiencing Coxsackie B infection, we may expect this serious condition to become more common and, if nothing is done, to occur in epidemic form.

Let us therefore look at the pattern of poliomyelitis in different parts of the world, regarding it not simply as a study of poliomyelitis but as a model of how we may expect other enterovirus infections to behave in the coming years. Of course we cannot expect this extrapolation to be correct in all details; for example, the probability that an infection will produce clinical disease in susceptibles of different age groups is not necessarily the same for different viruses. It may be that Coxsackie B tends to produce serious disease most frequently in infants, whereas poliomyelitis seems to produce paralysis least frequently in that age group. Figure 2[18] summarizes the

immunity status to poliomyelitis of populations in different parts of the world. I have departed from the conventional method of presenting these data because I think that this presentation shows more clearly the change in the rate of acquisition of immunity, or rather loss of susceptibility, in areas in different stages of development. Here you see the familiar pattern of rapid loss of susceptibility in areas of low standards of hygiene and sanitation, followed progressively by a slowing down of the process as these standards are raised, until in the most highly developed communities natural immuni-

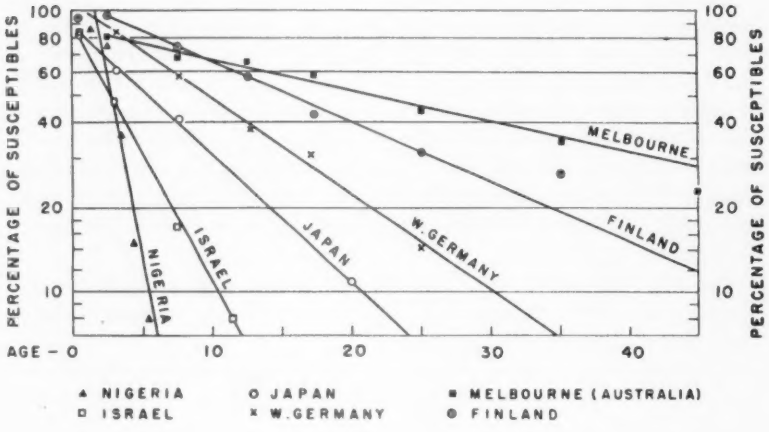

FIG. 2.

zation is a very slow process which may never be completed. I would like to emphasize that although on this figure reference is made to countries, in fact one may find the whole range shown within the same country in the different socio-economic groups, when there is a wide variation in economic status. This must be borne in mind when quoting a figure purporting to represent the country as a whole. At best it is only an estimate of the average situation, and if the population sampled is not well chosen, the result may be misleading. However, in many instances such investigations have proved useful and to correlate satisfactorily with the age incidence of paralytic disease when reasonably reliable figures are available for the latter. It is therefore justifiable to assume that information such as this enables one to predict the age distribution of an epidemic of paralytic poliomyelitis, should that occur. In practice that expectation has been borne out.

This information does not enable one to predict when an outbreak will occur, nor its probable severity. All one can say is that outbreaks are more likely the slower the rate of loss of susceptibility, and that they generally tend to be more severe. There is another indicator which is simpler, but probably less reliable. As shown in Figure 3, a fall in the infant mortality rate is associated with a marked rise in the mean incidence of poliomyelitis.[11]

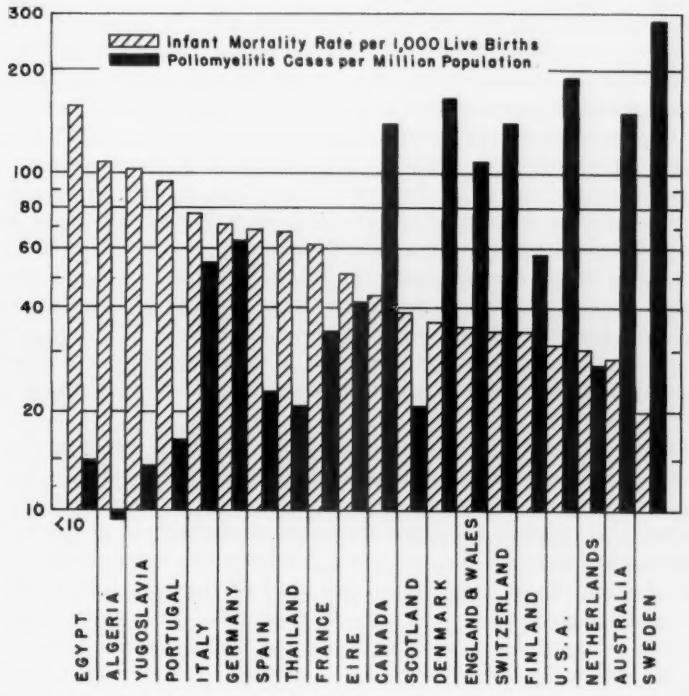

FIG. 3. Infant mortality rates, indicated by cross-hatched vertical columns; poliomyelitis cases, per million population, indicated by black vertical columns (adapted from Payne, ref. 11, p. 396).

Dr. Paul, in studies in South America,[9] has produced further evidence in support of this. Briefly, when the infant mortality rate falls below about 75/1,000 live births, one may expect the poliomyelitis incidence to increase to 3-4/100,000 total population. With lower infant mortality, the median incidence may become very much higher.

This is, however, by no means the invariable rule and recently very severe outbreaks have been observed in countries with high infant mortality

rates. It is necessary to look for another explanation of this phenomenon. In my opinion the pattern of epidemics in different parts of the world since the mid-1940's suggest that there has been a spread throughout much of the world of strains of type 1 virus of heightened virulence for the human nervous system. That this change, if it has occurred, has not been associated with any significant antigenic variation, is shown by the fact that the disease is practically confined to infants in those areas where that would be expected; older children and adults have been naturally immunized by the previously prevalent strains. It is indeed fortunate that poliovirus does not behave like the influenza virus. We are not entitled to say that that will never occur, but consideration of the history of poliomyelitis in the past and studies of the world situation today make it seem unlikely. However, we do not know how other enteroviruses will behave in this respect. If this interpretation is correct, it becomes a matter of urgency to be able to recognize strains of increased neurotropism, since they are those most likely to break through vaccination, as occurred recently in Israel. Unfortunately no simple tests are currently available. It is to be hoped that studies similar to those now in progress on genetic markers associated with low virulence might eventually lead to such a test. At any rate efforts should be made now to collect and preserve as near as possible in their original state the strains responsible for these outbreaks, so that they will be available for examination later.

I have said that these lessons should also be applied to the other enteroviruses. We need to know much more about the prevalence of these agents in different populations, the rate at which immunity is being acquired, and the antigenic structure of the prevalent viruses, especially those responsible for clinical diseases but also those not at present known to cause disease, since they may do so in the future. One hundred years ago one might well have doubted the pathogenicity of poliovirus for man had one been able to study it. We need this information so that we have a base line from which we can measure future changes which may give warning of impending trouble.

The epidemiological approach to many other different disease problems is similar in principle. As well as undertaking detailed epidemiological studies of individual diseases, we need to map the world distributon of potential pathogens, and to study their antigenic structure and other characteristics, and we need to know which are infecting man, at what rate this is taking place under different conditions, and what clinical disease is caused and with what frequency in different age groups.

Some of this information can be obtained from properly designed serological surveys and this led me to propose a multi-purpose approach to such

surveys, designed to provide the maximum amount of information from a given investigation. In order to study and advise on this proposal, WHO convened in December last year a study group,[16] among the members of which were a virologist, an epidemiologist, a bacteriologist, a veterinarian, and a statistician, as well as a biochemist-nutritionist and an expert on hemoglobins. The latter were included because it occurred to me that there are a lot of other things in blood besides antibodies, the investigation of which is of great importance in the study of health problems other than communicable disease, and that many of the epidemiological and statistical considerations in surveys for different purposes were likely to be similar in principle. These include nutritional disorders, anemias, human genetics (blood groups, abnormal hemoglobins), and others.

There are two main thoughts behind the proposed program. The first is that if sera are collected according to statistically sound sampling methods, so that they are truly representative of the population, then the past experience of the population with communicable diseases may be estimated by studying the antibody content of the sera, using a wide variety of antigens. The second is that there are many diseases prevalent today of which we do not know the cause and it is certain that new agents will be isolated and new clinical syndromes recognized in the future concerning which information regarding their past history will throw valuable light on the evolutionary trend. If, therefore, portions of these serum samples are stored under such conditions as to preserve antibodies, they will be available in the future for examination against antigens not yet discovered and, in comparison with future surveys, provide evidence of the changing immunity status of populations. A great deal of valuable information has already been obtained by the examination of the antibody patterns in different age groups. I have already mentioned the influenza and poliomyelitis studies. But it is easy to see that these collections would in the course of time yield much more definite information which would be easier to interpret.

This approach of course has its limitations. Different samples may be preferred for the study of different types of infection; some infections are sharply limited in their geographical distribution and the infected area may not have been included in the sample; in some instances owing to lack of specificity of the test used it will only be possible to identify the presence of members of a group of viruses and not the specific virus itself. However, even in the latter instance the survey is of value in identifying areas where further investigations are needed and the virus groups which should be given special attention. It must be recognized that, valuable though they may be, serological surveys give information on only one side of these problems. Other investigations will always be needed to complete the ecological picture.

In studying human disease it is sometimes forgotten that many human pathogens are also pathogens for various species of animals. In some infections animals are the primary hosts and infection of man an ecological accident of no significance for the survival of the agent. It is clear that studies of the ecology of human disease will not be complete without studies of the part played by animal infections. I have already mentioned the possibility that animals may play a role in the ecology of influenza. It would come as a surprise to many if eventually it were shown that influenza was primarily a zoonosis! I am not suggesting that that is so, but investigation of the possibility has hitherto been neglected. It is therefore proposed that the serological approach mentioned, including the establishment of collections of sera, would be applied to domestic and, as far as possible, to wild animals as well.

We have much to learn regarding the best way to carry out this rather ambitious project. Pilot studies will be needed and one has already been initiated in Africa, using the multi-purpose approach, including hematological and nutritional studies. It was interesting to find in one area that co-operation was obtained because of the information which would be obtained on nutritional problems and not on communicable diseases. If I had only been able to offer the latter, I doubt whether the survey would have been carried out.

Our plan is to encourage and support the establishment of reference banks of sera in centers conveniently located in different parts of the world. A central punch card index will be established so that information will be immediately obtainable as to what collections are available, the conditions under which they were made with full epidemiological data, and the examinations already performed, together with the results. Parts of these collections will be made available for approved investigations anywhere in the world. If, for example, in 1970 one of you should want to investigate the prevalence of a particular agent (perhaps one not yet discovered) in Africa, say, in Kenya in 1959 or in Nigeria where we did our first pilot study in 1956, we would be able to locate and provide you with the necessary material.

I hope I have shown you that many, if not all, communicable diseases, and many other diseases as well, are ultimately international problems and that a full understanding of the changing patterns of disease can only be attained by international co-operation and coordination of effort. This understanding is needed for the protection of all peoples from the possible undesirable consequences of man's massive interference with the ecological situation in which he lives, as well as for the improvement of the lot of humanity now. We do not want to risk our civilization ending in the same way as earlier ones through our own fault.

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STUDIES ON THE ECOLOGY OF ARTHROPOD-BORNE (ARBOR) VIRUSES**

It is a curious fact that the first disease in man proven to be caused by a filterable virus is arthropod-borne—I refer of course to yellow fever—and yet today our knowledge of this category of viruses, particularly as concerns the epidemiology of human infection, is less complete or more obscure than any of the other main virus families.

There are reasons for this: the infection does not pass directly from one human being to the next and therefore cannot be traced by this simple means; there is always an intervening vector or arthropod, and in most instances one or a number of intervening lower vertebrates. Indeed, with a few notable exceptions, man is not involved in the cyclic propagation of these viruses. His infection is tangential, fortuitous, and usually dead-end. It may be compared to that of a bystander at a ball game who gets hit by a foul ball. His social rank, his economic status, his food, his physical state, and his association with his fellow man are of little moment in the epidemiology of his infection. What counts is his exposure to the bite of an arthropod carrying the virus.

Thus, to understand the epidemiology of these infections in man, we must know when and where they occur and the arthropods and lower vertebrates involved in their propagation—in short, we must be familiar with the ecology or life cycles of these viruses.

In our opinion the outstanding problems to be tackled for a better understanding of these viruses are the following:

Search for as yet unknown viruses in this category. It is only in recent years that concerted efforts have been made to search for these viruses in their arthropod vectors and lower vertebrate hosts. These efforts have been rewarding, particularly in the humid tropics. New ones are constantly being discovered and further search with improved methods will undoubtedly yield more. Also, it should be remembered that the exact etiology of a large

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portion of human encephalitis occurring each year in the United States remains undetermined. The clinical manifestations and the cytological response of many of these cases suggest a viral infection. It is quite likely that some of them may be caused by as yet undiscovered arthropod-borne viruses.

Identification of the arthropods and vertebrates actively involved in the cycles of these viruses and discovery of means of their survival during the inactive transmission season. A good deal is known about the ecology of some of the long recognized arthropod-borne viruses, but even with these our knowledge lacks precision, and the natural history of all of the newly discovered ones remains to be unraveled.

Classification and geographical distribution are essential in order to appreciate the interrelation and the global epidemiology and to evaluate the potential threat of these infections. There is reason to suspect that the birthplace and permanent home of many of these viruses is in the tropics, and that they have been secondarily emplanted in the temporate zones. An example will be given in discussing the ecology of Eastern equine encephalomyelitis (EEE).

Manner of dissemination. It is known that birds are hosts to many of these viruses, and it is suspected that they may play an important part in their long-range implantations. This concept demands further attention. Again, EEE, to be referred to later, may be cited as an example.

The importance of determining the pathogenicity of these viruses particularly in man is self-evident and when a new viral agent is isolated, especially from arthropods and lower vertebrates, the questions that immediately arise and should be investigated are: Is it infectious to man? What is the symptomatology? How frequent and under what conditions does infection take place?

Methodology should be given a major rating because success in solving the above-listed problems will depend in large measure upon the discovery of new methods and the refinement of the old.

Our studies here at Yale are concerned to some degree with all these problems. They consist of:

The study of the ecology of eastern equine encephalomyelitis (EEE) in the Connecticut area. In New England EEE has in the past produced costly epidemics in horses and pheasants and occasionally has been the cause of human encephalitis, always severe and frequently fatal. It remains a constant threat.

This virus has for many years received the attention of other investigators and a great deal has been learned about its natural history, in which birds

FIG. 1. The shading on the map represents the principal areas where Eastern equine encephalomyelitis (EEE) has been reported. The following sources were used. For distribution in U.S.A.: Report on surveillance of arthropod-borne encephalitis in the United States, June 16, 1958, Communicable Disease Center, Atlanta, Georgia. For Latin America: Plate 13, Explored areas of arthropod-borne viral infections, American Geographical Society; Downs, W. G. *et al.*, *Amer. J. trop. Med.*, 1956, *5*, 626; Causey, O. R. and Theiler, M., *Amer. J. trop. Med.*, 1958, *7*, 36; Alice, F. J., *Rev. bras. Biol.*, 1951, *11*, 125 (including references to other Brazilian publications). Some liberty has been taken in outlining infected zones in South America by including areas of similar biological environment contiguous with places where the presence of the virus has been recognized and reported.

and mosquitoes seem to be mainly involved. Its geographical distribution, so far as is known, is illustrated in the accompanying map. As will be seen from the map, infection by this virus has been recognized mainly along the east and southern border of the United States, the east coast of Mexico, Panama, Cuba, the Dominican Republic, and the northern coast of South America and Brazil. Recent studies indicate that it is endemic in the Amazon rain forests. Those familiar with the flyways of migrating birds will immediately recognize similarities in the pattern of the distribution of this virus and the main eastern flyways of certain migratory birds. However, there is still a good deal to be learned to understand completely the behavior of this virus.

Our studies involve obtaining further information on the life cycle of the virus, the vectors and vertebrate hosts involved, the determining factors in epidemics, and the question of the virus 'overwintering' or being implanted each season by migrating birds. Fortunately for the pheasant farmers but unfortunately for our studies, there has been little evidence of the activity of the virus in this area since the studies were begun in the summer of 1956.

However, some evidence has been obtained which suggests that the virus does not overwinter in hibernating mosquitoes, and if the virus does overwinter in this area, we believe some other mechanism must be involved. We are now investigating the possibility of a hitherto unsuspected cycle in non-blood-sucking insects as a mechanism of survival of the virus and for explaining the sporadic infections which seemingly occur during the nonepidemic years. It has been found that larvae of insects common in this region (such as the beetle *Tenebrio molitor* which in the larval form is frequently referred to as the yellow meal worm) are susceptible to infection by parenteral inoculation and through food, and that nestling birds may be infected by consuming these infected larvae. It has also been found that the infection in the larvae may be carried from the larval through the pupal to the adult form of the insect. The question of the virus being passed from one generation of this beetle (*T. molitor*) to the next is now under study.

Isolation of a "new" virus. As a by-product of the EEE study, at least one virus has been isolated from a nestling bird which, according to investigations so far completed, may represent a new or rather a previously unrecognized virus. It has been tentatively designated as *Hilo* virus. The ecology of this virus, including search for evidence of human infection, is now under study and promises to be of considerable interest.

The antigenic classification and behavior in tissue culture of virus strains isolated in Egypt and the Sudan. This study, now nearing completion, involves 20-odd *Phlebotomus* (sandfly) fever strains and about an equal num-

ber of strains that are harbored and transmitted by ticks. Among these latter there appear to be 4 and probably 5 hitherto undescribed viruses distinguishable by their antigenic characteristics, arthropod and vertebrate host range and to a degree by their behavior in tissue culture. Two of these tick viruses are transmitted by *Argas* ticks, a variety that normally parasitizes birds. Birds seem to be the main vertebrate hosts of these viruses. Incidentally, the principal bird host of one of these viruses in Egypt, the cattle egret or *Bubulcus ibis ibis,* has in recent years appeared on this continent and has now become numerous in southern Florida. One wonders if the virus was also introduced. It is worthy of investigation since the virus which infects these birds in Egypt is also infectious to man.

The application of tissue culture (TC) to the study of the arthropod-borne category of viruses. These studies have been under the supervision of Dr. Henderson,[1] and in our opinion the results have been most encouraging. It has been possible by the use of various types of primary cell lines to cultivate virtually all of the prototype strains representing the major sero-groups of the arthropod-borne viruses, and, in addition, many ungrouped viruses including sandfly fever strains which had not hitherto been grown in tissue culture. The overlay plaque technique has been found most useful in detecting growth and for virus titrations. We are hopeful, therefore, that tissue culture may prove to be a valuable adjunct in:

1. *Isolating arthropod-borne viruses.* By selecting the proper cell line and utilizing the overlay plaque technique for revealing growth, it has been found that most of the viruses studied can be detected in as minute amounts as with the infant mouse method. It is also quite possible that, as with the enteric and respiratory virus families, tissue culture may uncover types of arthropod-borne viruses which have heretofore escaped detection. Indeed, the "new" virus (*Hilo*) encountered during the EEE studies was isolated in tissue culture, and could not be isolated from the original material by inoculation of infant mice.

2. *Performing neutralization tests.* The tissue culture method has proven useful in performing neutralization tests with several of the recognized arthropod-borne viruses, particularly those belonging to sero-group A. We are currently using it in our EEE investigations and in studies on Hilo virus. And we believe that the choice of suitable cell lines and the use of the overlay plaque technique will lead to a much broader application of tissue culture for neutralization tests among the arthropod-borne viruses.

3. *Classifying the arthropod-borne viruses.* The following tabulation of the behavior of 23 virus strains belonging to three different sero-groups in

chick embryo, Pekin duck, and rhesus monkey kidney tissue culture illustrates how tissue culture may be employed for virus classification. It is obvious that viruses of sero-groups A have the widest growth spectrum in that members of this group may grow on all of the three cell lines used, while those of group B are limited largely to growth on Pekin duck kidney and will not grow on chick embryo; group C, the most exacting of all, grow only on monkey kidney cells. The tabulation also illustrates the superiority of the overlay plaque method for detecting virus growth, especially in B and C sero-groups.

Virus sero-group	*No. virus strains examined*	*No. strains forming plaques and CPE*					
		CE		*PDK*		*RMK*	
		CPE	*PL*	*CPE*	*PL*	*CPE*	*PL*
A	10	7	*8*	4	10	7	10
B	8	0	0	3	*8*	0	1
C	5	0	0	0	0	0	*5*

CE—Whole decapitated chick embryo tissue culture.
PDK—Pekin duck kidney tissue culture.
RMK—Rhesus monkey kidney tissue culture.
CPE—Cytopathogenic effect observed in monolayer fluid phase cultures.
PL—Plaque formation in monolayer agar overlay cultures.

In conclusion the question might be asked why we at Yale should bother with these arthropod-borne viruses since for the most part they involve insects, birds, and lower mammals, and human infection with most of them is accidental. Admittedly, infection of man by these viruses, particularly in temperate zones, is much less frequent than by those viruses which require no intermediate host and circulate within the human population by direct transfer. However, we believe that these arthropod-borne viruses deserve attention for the following reasons: diagnosed, and probably a much larger number of undiagnosed, infections associated with severe and sometimes fatal encephalitis occur each year in North America; several epidemic outbreaks of St. Louis and Eastern and Western equine encephalomyelitis have occurred in the past and unless prevented may be anticipated in the future; arthropod-borne virus infections are much more frequent in the humid tropics and hitherto unrecognized members of this category are being constantly discovered, and the danger of these "new" viruses being implanted in temperate zones should be anticipated, and, if possible, prevented or controlled; two of the long recognized arthropod-borne viruses—yellow fever

and dengue—are endemic in South America, and there is a continuous threat of their introduction into our southern states. Here we have an excellent example of the fruits of research, for if it were not for the knowledge gained by research on methods of controlling these two infections if introduced, they would indeed constitute a very grave health hazard. Finally, these arthropod-borne viruses with their frequently complicated life cycles and their divergent vagaries offer the inquisitive investigator, with an ecological bent, many fascinating and intriguing problems to exercise his talents.

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THE EPIDEMIOLOGICAL VIRULENCE OF STAPHYLOCOCCI

INTRODUCTION

It has become apparent in recent years that exposure to the hospital environment can give rise to serious, sometimes fatal infection by hemolytic staphylococci. It is the purpose of this report to present data on the incidence of staphylococcal disease in human populations and to review evidence for unusual virulence in man of so-called hospital staphylococci.

Among many factors which have been thought to account for the apparent increase in nosocomial infection, four are predominant:

1. Advances in therapy have permitted prolonged survival of many patients with debilitating diseases. Hospital populations are coming more and more to consist of chronically ill, often elderly individuals who enter because of complications of disease or its treatment. The exposure of an increasing number of susceptible patients to the staphylococci that abound in the institutional environment has tended to favor development of serious infections.

2. Reliance upon antibiotics has undoubtedly led in many institutions to lowering of standards of cleanliness and neglect of techniques of asepsis and isolation, facilitating transmission of bacteria from hospital reservoirs to patients.

3. Staphylococci and other antibiotic-resistant organisms now abound in hospitals in great numbers. When a human population is exposed to an antibiotic, its bacterial flora is disturbed and eventually altered in favor of bacteria resistant to the drug. In Norway, where staphylococcal infections have been reportable for years, Lindan and Lofkvist[18] documented a striking increase in the frequency of staphylococcal infections of the newborn a few years after the introduction of the sulfonamides and penicillin. It has been shown that hospitalized patients are carriers of staphylococci more frequently than are nonhospitalized persons.[20] Knight *et al.* found that the carrier rate increases with the length of stay in the hospital and that patients who are treated with antibiotics are particularly likely to acquire staphylococci from the hospital environment.[12] Rountree and Barbour[15] were among the first to demonstrate that hospital personnel exposed to patients of this type develop higher carrier rates.

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4. It has been suggested that the staphylococci encountered in hospitals at the present time have greater virulence than those encountered in the pre-antibiotic era, or in nonhospitalized persons.

Virulence refers to the relative ability of an organism to produce disease. It is a controversial and ill-defined term, thought by some to be synonymous with pathogenicity. Virulence is dependent upon a number of factors (toxins, host, portal of entry, and so on), and is commonly measured by the number of organisms required to produce disease in a given system. Biochemical correlates of staphylococci such as pigment, hemolysin, and coagulase production are clearly not precise enough to estimate degrees of virulence for man. By means of bacteriophage typing, many staphylococci can be classed into strains, and an epidemiological estimate of virulence has become possible.

THE CONCEPT OF AN EPIDEMIC STRAIN

When hospital staphylococcal infections first began to receive attention, antibiotic-resistant strains belonging to the broad phage group III were generally incriminated.[11] In 1955, Rountree and Freeman[16] reported the isolation of a then nontypable and presumably uncommon strain from a nursery epidemic in Australia, and in 1956 the isolation of the same strain in Canada was reported by Bynoe *et al.*[3] This organism is a coagulase and mannitol positive hemolytic *Staphylococcus aureus* with the phage type 52/42B/47C/44A/80/81. It has recently been designated type 80/81. It is almost always highly resistant *in vitro* to the action of penicillin, streptomycin, and the tetracyclines, and usually susceptible to vancomycin, neomycin, bacitracin, kanamycin, erythromycin, novobiocin, and chloramphenicol. In the past two or three years this strain has become notorious because of the frequency with which it has been reported as the etiologic agent in hospital epidemics in the United States and many other parts of the world, and it is often loosely designated as "the epidemic strain." The question has naturally arisen as to whether this strain has been isolated so frequently from epidemics because it has an unusual propensity to incite disease or because it is merely commonplace in hospitals.

THE BEHAVIOR OF TYPE 80/81 IN HUMANS

There is a considerable body of information in the literature suggesting that type 80/81 has a greater tendency than many other strains of hemolytic staphylococcus to produce disease in infants and young children. In a nursery epidemic studied by Fekety *et al.*,[7] 34 of 49 (70 per cent) of the newborns who became carriers of the strain developed clinical infections

within the first few months of life. In contrast, only 3 of 92 (3 per cent) infants colonized by other coagulase-positive staphylococci developed clinical illness during the same period. In a similar outbreak reported by Wysham *et al.*[20] 78 per cent of the infants colonized by strain 80/81 developed clinical manifestations of infection, while only 31 per cent of those colonized by other staphylococci developed disease. They suggested that type 80/81 was of unusual virulence, but that it was not the only virulent strain in their nursery. Shaffer[19] and Wentworth[21] have reported similar attack rates for type 80/81 in newborns. In addition, the clinical observation has been made that type 80/81 has a tendency in infants to produce pneumonia, empyema, mastitis, and severe spreading cellulitic infections somewhat different from the characteristic abscess.[8, 10]

It has been suggested that the strain may be unusually virulent only for infants, and that the nursery may be the source from which the strain is disseminated to other parts of the hospital. There is evidence that the peculiar disease inciting powers of the strain are not limited to the nursery, however. Wentworth *et al.*[21] have studied the spread of this strain after its introduction into the family and community by the newborn. They have been impressed by the frequency of its transmission to family contacts, by the severity of subsequent infections, and by the stubborn persistence of the strain in the afflicted family. During their study, in 45 per cent of the families of infants who had been ill, one or more members developed suppurative disease, while only 9.5 per cent of the families without such contact had a similar experience.

Additional evidence that the strain behaves in an unusual manner even in otherwise healthy young adults was obtained during an investigation of an epidemic of type 80/81 infection in students at the veterinary school of a large university.[3] Many of the students had severe, recurrent skin infections, and the exact source of the outbreak was not determined. A survey showed that approximately 5 per cent of a group of controls recalled skin abscesses within the six months prior to being questioned. Gould and Cruikshank[9] reported similar rates for healthy persons. Ten per cent of the veterinary students who were subsequently found to be carriers of coagulase-positive staphylococci recalled such infections, but more than 50 per cent of those found to be carriers of type 80/81 recalled skin abscesses within the preceding six months.

Another example of the behavior of strain 80/81 in healthy adults was afforded by our studies on the persistence of carriage of staphylococci in the anterior nares of nurses and doctors from several hospitals. Cultures were taken at least once per week, and only those who carried the same strain for more than three weeks were included in the study. The results are shown in

Figure 1. There were 25 persistent or permanent carriers of type 80/81. The mean duration of carriage of the strain was 5.5 months, and many of the individuals were still carriers when the study ended. In contrast, the mean duration of carriage of other coagulase-positive staphylococci was only 3

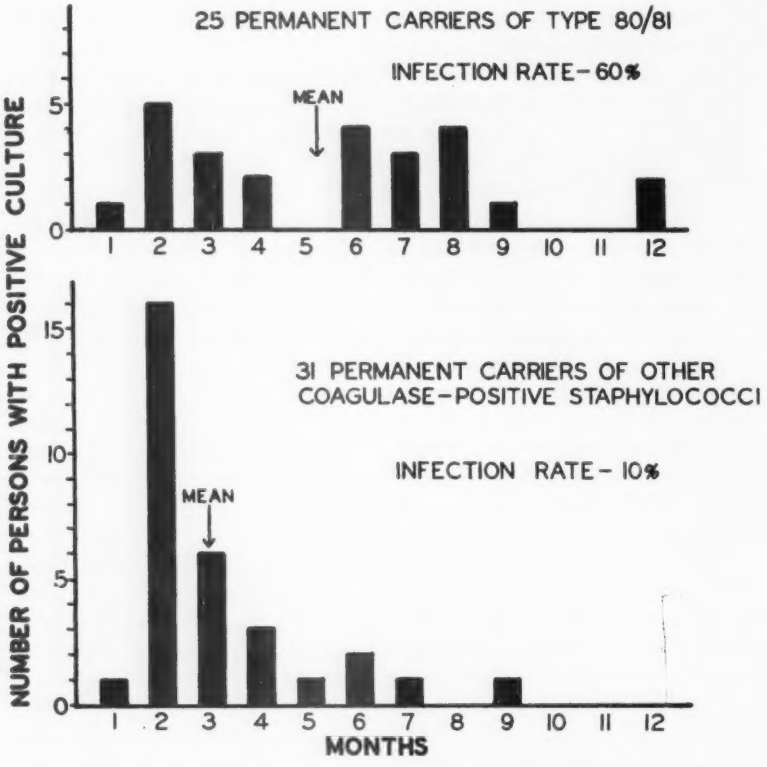

FIG. 1. The persistence of staphylococci in the anterior nares of adults.

months in 31 persons studied. During the period of observation 60 per cent of the persons carrying type 80/81 developed suppurative disease, while only 10 per cent of those carrying other strains were so afflicted. All of the type 80/81 carriers had been removed from the area in which they had presumably acquired the strain, though many of them probably were still exposed to the organism from time to time. Many of these presumably healthy individuals who were plagued by recurrent infections have been unable to rid them-

selves of the strain notwithstanding treatment with appropriate systemic antibiotics, the use of nasal antibiotic creams, and the adoption of various general hygienic measures. Many persons will respond to such treatment, but those who do not, give impressive testimony to the belief that it is not the lack of conventional immunity conditioned by prior experience with the organism which is responsible for the high rate of clinical illness observed.

In our studies concerning the kinds of staphylococci prevalent in a large general hospital under nonepidemic conditions, it was shown that although patients were being exposed to many different strains of staphylococci, type 80/81 was the one most commonly associated with disease. All of the staphylococci isolated from inpatients and outpatients at the clinical bacteriology laboratory of the Johns Hopkins Hospital from August 1, 1957 to April 30, 1958 were obtained by us and typed according to the bacteriophage method of Blair and Carr[1] using 25 phages. There were 900 isolates of *S. aureus* on which data sufficient for this analysis are available, and 75 per cent of these were typable. Although roughly 64 different strains were encountered, 31 per cent of the isolates were classed as type 80/81. There were 498 organisms from clinical infections, and 253 or 50.8 per cent of these were type 80/81. There were 402 isolates from the nose and throat, and the vast majority of these were asymptomatic infections not associated with suppurative disease elsewhere. Only 24 or 6.0 per cent of the isolations from the nose and throat were type 80/81. In 91 per cent of the instances in which type 80/81 was isolated, it was from a clinically recognized infection. In other words, type 80/81 isolates constituted a far greater proportion of the cultures from clinical infections than it did of the cultures from asymptomatic carriers. One conclusion which might be drawn is that type 80/81 organisms have a greater than average tendency to manifest their presence in a colonized host by a clinical infection. These results are summarized in Table 1. Since no other single type was encountered in appreciable numbers, the organisms there are divided into broad phage groups. Nontypable staphylococci, previously considered to be relatively nonpathogenic, were more outstanding in the nose and throat cultures than in those from infections. Although it was recognized that they are a heterogeneous group on the basis of antibiotic sensitivities, nontypable organisms were exceeded in frequency of isolation from clinical infections only by type 80/81.

Further examination of the data even more impressively implicated type 80/81 as the cause of hospital cross-infection during this study. Although only 31 per cent of the organisms isolated were type 80/81, 75 per cent of the clinical infections due to antibiotic-resistant organisms which had their onset after admission to the hospital were due to type 80/81. It should be emphasized that this study was performed under nonepidemic conditions.

TABLE 1. STAPHYLOCOCCI ENCOUNTERED AT THE JOHNS HOPKINS HOSPITAL AUGUST 1957 TO APRIL 1958

Type of staphylococcus (Blair and Carr[1])	*Total isolations*		*Isolations from infections*		*Isolations from the nose and throat*		*Per cent isolation of the strains from infections*
	Number	*Per cent of total*	*Number*	*Per cent of infections*	*Number*	*Per cent of nose and throat isolations*	
Group I	100	11.1	44	8.8	56	13.9	44
Group II	73	8.1	29	5.8	44	11.0	40
Group III	153	17.0	60	12.3	93	23.1	39
Nontypable	220	24.4	83	16.6	137	34.1	38
Miscellaneous	72	8.0	24	4.8	48	11.9	33
Type 80/81	275	30.6	253	50.8	24	6.0	91
Total	900	...	498	...	402	...	55

Only 1.5 per cent of the hospitalized patients developed staphylococcal infections. The cases were distributed evenly through the course of the study without concentration on a particular ward or service, and nursery infections were rarely encountered. A culture survey one month before the end of the study showed that approximately 5 per cent of the ward personnel and 4 per cent of the patients carried type 80/81. While staphylococci could be isolated with ease from the air, walls, floors, blankets, etc. in the hospital, type 80/81 was infrequently encountered in these sites. Under these endemic conditions one might have expected to isolate a variety of strains from the patients with infection. Since this was not the case, these data suggest that type 80/81 staphylococci were inordinately frequent agents of hospital infection, and that the strain therefore has greater virulence than many other coagulase-positive staphylococci.

DISCUSSION

Certain facts appear to be inconsistent with the thesis that type 80/81 has unusually virulent characteristics. McDonald[14] has studied a nursery where a high rate of colonization with the strain was followed by a low rate of subsequent illness. This staphylococcus was said to be identical in all measurable respects to the classical type 80/81; but since there may be variation within a type, these strains may not be identical. However, it is conceivable that the enhanced virulence we observed may be related to passage of the strain in human lesions.

It has not been possible to demonstrate that other staphylococci sharing the biochemical characteristics of type 80/81 are less virulent than it is for laboratory animals. However, Selbie and Simon[17] have presented data suggesting that the most important *in vitro* property related to the virulence of staphylococci for mice is alpha-hemolysin production; and Shaffer *et al.*[18] reported that only 6 per cent of 310 strains tested produced more alpha-hemolysin than did strain 80/81.

Elek[4] found that a million or more staphylococci were required to produce an infection in the skin of man following an intradermal inoculation, and that no differences could be found in the virulence of nasal or "lesion" strains, including one unidentified epidemic strain.[5] Since it is unlikely that most human infections are initiated by contact with a million or more staphylococci, it is probable that some host factor (such as an effect of skin oils or some condition at the base of hair follicles) permits the organism to multiply until it is able to overcome host defenses. Elek[4] found that the ability of his strains to initiate infection was enhanced five hundred fold by a suture at the site of inoculation, and he concluded that the circumstances of

the infection rather than the virulence of the organism determined the issue. However, if these circumstances or host factors favor a given strain more than others, it seems quite proper to refer to that strain as more virulent, for virulence always implies an interaction with the host. If one wishes to determine what it is about the host that is critical, it is then important to recognize that such factors may be particularly related to certain staphylococci.

Williams[22] has recently stated that the idea that all coagulase-positive staphylococci are of similar virulence can no longer be held. The data presented here suggest that type 80/81 is an unusually virulent staphylococcus, but it is by no means meant to imply that it is the only staphylococcus of increased virulence for man. Many recent epidemics have been traced to other strains, though type 80/81 has remained the outstanding epidemic strain.[23] Since it has not been possible to relate the virulence of type 80/81 to the number of organisms required to produce infection within the tissues, this property should be termed *epidemiological* virulence in order to avoid confusion with the term employed in animal studies.

Gillespie[6] briefly mentioned a hospital population colonized by an antibiotic-sensitive type 80/81 which appeared to be relatively avirulent, but there is no evidence that staphylococci made resistant to antibiotics *in vitro* thereby acquire enhanced virulence for animals or man. Similarly, there is no good evidence that the virulent antibiotic-resistant staphylococci encountered now are any more or less virulent than the virulent antibiotic-sensitive staphylococci encountered in the pre-antibiotic era,[2] and it does not seem likely that such data can be obtained. It does seem probable that virulent staphylococci have recently become more numerous, and that hospitals in particular have been seeded with these organisms, partly because of the frequency with which antibiotics are used there. Elek[6] has stated that "hospitals must be the Mecca of all truly virulent staphylococci, for the more severe the lesion, the more likely it is that the victim will make his pilgrimage to the hospital." The goal of further investigation is to prevent this strain from parasitizing new victims within the hospital.

SUMMARY

Type 80/81 staphylococci have gained recognition because of the frequency with which they have been associated with epidemics of suppurative disease in hospitals. The colonization of newborns by the strain is followed by an unsually high rate of clinical illness in the infants and their family contacts. Healthy adults appear to be unusually susceptible to the strain, for the strain persists for relatively long periods in the nares of adults and is associated with clinical illness in more than half of such cases. In one hos-

pital, the strain was isolated from 75 per cent of the cross-infections due to antibiotic-resistant staphylococci during a nonepidemic period when the strain represented a small segment of the staphylococcal flora of the hospital. It was concluded that the strain behaves epidemiologically as if it were more virulent than many other coagulase-positive staphylococci. Other staphylococcal strains with similar virulence probably exist, and there is no good evidence that these organisms acquire enhanced virulence for man when they become resistant to antibiotics.

The high frequency of hospital staphylococcal infections is related to the fact that virulent organisms have become more numerous in hospitals, in part because the spread and acquisition of such strains is facilitated by antibiotics. Many patients in hospitals are unusually susceptible to infection, and lapses in techniques of cleanliness and asepsis have increased their contact with bacteria. All of these factors must be taken into consideration if hospital staphylococcal infections are to be prevented.

ACKNOWLEDGMENT

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ASIAN INFLUENZA IN NEW HAVEN, 1957-1958: AN EPIDEMIOLOGICAL SURVEY†

The appearance of the new Asian influenza virus in early 1957 and its subsequent rapid spread throughout the world stimulated renewed interest in the epidemiology of influenza. For the first time since identification of the etiologic agents of this disease the opportunity presented itself for study of its pandemic form by specific microbiological tests. The results of a number of such studies concerning various epidemiological aspects of Asian influenza have now been published.[3, 5, 8, 16, 20, 26, 30]

The study on which this report is based provided information which further documented attack rates and other epidemiological features of Asian influenza. In addition, some data were obtained concerning the relationship of certain local socio-economic factors to the pandemic.

MATERIALS AND METHODS

In the spring of 1957 a longitudinal serological survey for antibodies to various infectious agents was begun in the New Haven area by the Section of Epidemiology and Preventive Medicine. In May and June of that year, before Asian influenza had made its appearance in Connecticut, serum samples were obtained from about 1,100 school children, adolescents, and adults. Approximately a year later, several months after the pandemic had subsided, about 500 of the same individuals were bled again. At the time of the second bleeding these individuals or their parents were asked if they had been vaccinated against Asian influenza and if they had had influenza during the preceding year. Unfortunately, only a relatively small number of adults were bled a second time; most of these worked in a single factory and nearly all had been vaccinated against Asian influenza. For this reason the study is mainly concerned with juvenile rates. A total of 286 subjects with paired sera were studied and, except for the adults, practically all of whom were included, were chosen on a random basis according to age and social class.

Table 1 shows the study population, divided according to age and social class. There were no infants or preschool children included in the study, and the adult group, consisting mostly of individuals in the third and fourth decades of life, did not include any older individuals, that is, beyond the fifth decade. There was a fairly even

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distribution according to age and social class except for the adult group where there were relatively few in the upper social class.

No exact data were available concerning the details of vaccination, or concerning the illnesses experienced by those who said that they had had Asian influenza. Information of a general nature, however, indicated that most individuals in this area, who received Asian influenza vaccine, were given one or two intracutaneous injections of 0.1 cc. of a monovalent preparation containing 200 CCA units per cc. during the fall of 1957. Additional data indicated that the vast majority of clinical influenza in Connecticut occurred during the fall, with the peak incidence in the third week of October.[11] This was similar to the experience throughout most of the U.S.A.,[10] and is well illustrated by the curve for excess deaths from influenza and pneumonia, which, after a short lag period, paralleled that for the reported incidence of influenza during the fall.[7] Figure 1 depicts the graph for these excess death rates in 14 New England cities, in relation to the times at which serum samples were obtained.

TABLE 1. TOTAL SUBJECTS STUDIED, DIVIDED ACCORDING TO AGE AND SOCIAL CLASS

Age group	*Social class*	
	Lower	*Upper*
5-9	33	36
10-14	41	45
15-19	37	30
20-59	44	20
Totals	155	131

Samples of sera were separated from the clots on the same day on which blood was obtained, frozen in several aliquots, and stored at —20° C. Paired sera from each individual were examined simultaneously in the same test, using dilutions of 1 in 4 through 1 in 64, for both complement-fixing (CF) and hemagglutination inhibiting (HI) antibodies. Allantoic fluid preparations of early egg passages (5th, 6th, or 7th) of the A Japan/305/57 strain of Asian influenza virus were used in all tests. In agreement with the report of Meyer, this strain was found to be insensitive to the non-specific inhibitors of hemagglutination present in human sera.[20] Consequently, no attempt was made to remove these inhibitors, and the sera were treated only in that they were heated in a water bath at 60° C. for 20 minutes. The tests for HI antibodies were done by the method recommended by the Committee on Standard Serological Procedures in Influenza Studies.[8] The CF tests were done according to the modified plate technique of Fulton and Dumbell, using one and a half units of guinea pig complement and eight units of antigen.[24] Only sera showing a four-fold or greater rise in titer, from 1957 to 1958, by one or both tests, were considered positive, that is, were considered to have shown a significant rise in antibody.

RESULTS

Prevalence of pre-pandemic antibodies and comparison of CF and HI tests in determining antibody rises. As was to be expected, Asian virus HI anti-

bodies were not found in any of the 1957 or pre-pandemic samples of sera, because relatively few adults and no individuals beyond the fifth decade were included in the study.[8, 20, 21] On the other hand, pre-pandemic sera of about 40 per cent of the subjects contained CF antibodies, indicating prior antigenic experience with at least one of the influenza A viruses. Furthermore, in confirmation of the work of Davenport and others, it was found that the prevalence of CF antibodies in these sera increased progressively

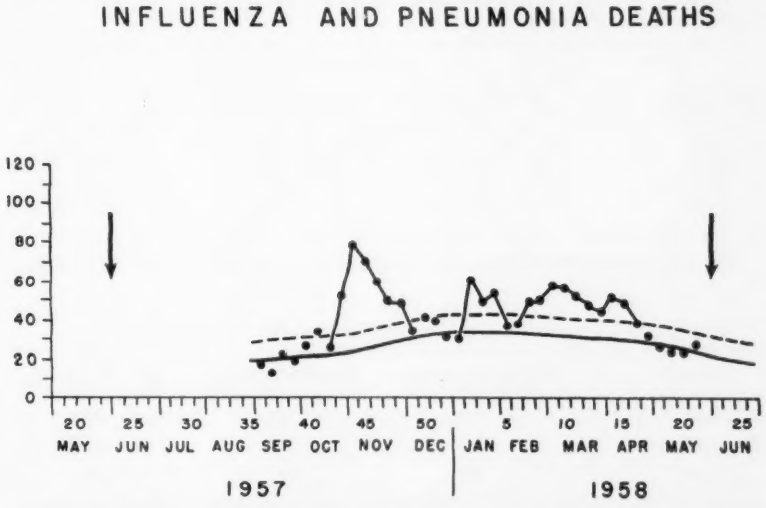

FIG. 1. Chart showing excess mortality from influenza and pneumonia in 14 New England cities, during and following the Asian influenza pandemic. Blood samples were obtained in New Haven, as indicated by the arrows, in May-June 1957 before the pandemic began and again in May-June 1958 after it had subsided. The seasonal trends are shown by the parallel lines, the solid line representing "normal incidence," and the broken line, the "epidemic threshold." (Reproduced, with the kind permission of Dr. M. Pizzi, from CDC Influenza Surveillance Report, No. 41, May 29, 1958.)

with age.[8, 12] This is well illustrated in Table 2 which shows the age-specific prevalence of CF antibodies. The possession of these CF antibodies, however, afforded no protection against infection with the Asian virus, since the incidence of antibody rises, in unvaccinated individuals, was as great in those with as in those without such antibodies. Comparison of the CF and HI tests indicated that more rises were demonstrated with the former than with the latter, but that the greatest number of rises was observed when both tests were employed. In only about a third of the positive cases could a diagnostic rise in titer be shown by both CF and HI tests. Although the

techniques of testing differed somewhat, the results of the comparison were in accord with those obtained by Jensen,[18] Buebendorf,[4] and Kalter.[18] In contrast to the findings of these investigators, however, Jordan found more antibody rises with the HI test than with the CF test.[34]

Antibody rises in vaccinated versus unvaccinated subjects. Table 3 shows the cumulative totals and those for vaccinated and unvaccinated groups.

TABLE 2. AGE SPECIFIC PREVALENCE OF CF ANTIBODIES AGAINST INFLUENZA A IN PRE-PANDEMIC SERA

Age group	*Number tested*	*Number positive**	*Per cent positive*
5-9	69	12	17.4
10-14	84	22	26.2
15-19	69	36	52.1
20-59	64	40	62.5

* Positive denotes the presence of CF antibody in serum diluted 1 in 4 or greater.

TABLE 3. VACCINATION AND RISES IN ASIAN INFLUENZA ANTIBODIES

Groups	*Number tested*	*Number positive**	*Per cent positive*
Vaccinated	146	62	42.5
Unvaccinated	140	91	65.0
Totals	286	153	54.5

* Positive denotes a 4-fold or greater rise in antibody between 1957 and 1958.

More than half of all the individuals tested showed a significant rise in antibody, and there was more than a 20 per cent difference between the percentages in the two groups, (42.5 per cent of vaccinated and 65 per cent of unvaccinated subjects), thus suggesting that vaccination did exert some protective effect. The same data are depicted in Figure 2 which shows the percentage of individuals with antibody rises plotted against age. The numbers denote the total of all individuals studied in each group. The solid line represents vaccinated individuals and the broken line those who were not vaccinated. It is apparent at once that more than half of all persons studied showed a rise in Asian influenza antibodies. In agreement with the experience of others, the incidence of antibody rises was found to be greater in persons of school age than in those over the age of 20.[9,34] There was, however, no significant difference in incidence among the various younger

age groups. In the unvaccinated groups antibody rise obviously represented the incidence of Asian influenza infection, whereas in the vaccinated groups it may have been due, in part at least, to an antibody response to the vaccine. The high incidence—about 70 per cent—of infection among unvaccinated elementary and high school students is comparable to that of 75 per cent found by Carey among similar groups following the first U.S. community-

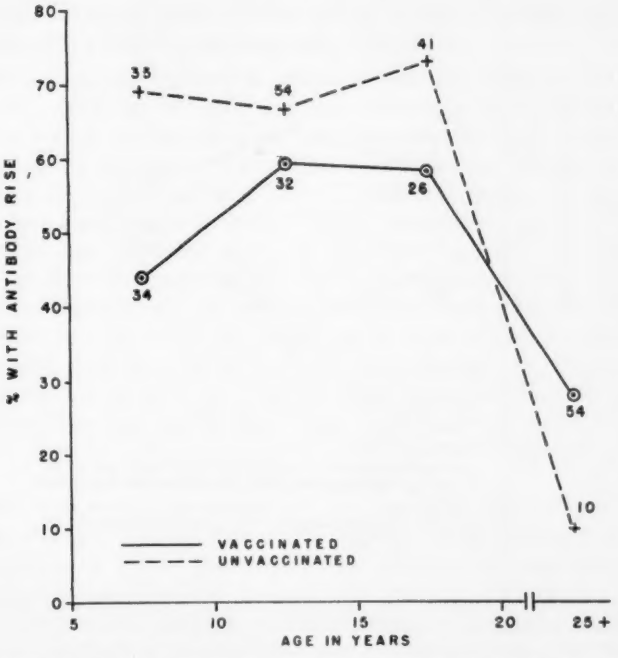

FIG. 2. Vaccination and age-specific rises in Asian influenza antibodies. Numbers represent total individuals tested in each age group.

wide outbreak of the disease which occurred in Louisiana in the summer of 1957.[5] There was little difference in antibody rise between vaccinated and unvaccinated in any of the different age groups. However, the incidence of rises in all groups except the adults was consistently less in the vaccinated than in the unvaccinated.

History of Asian influenza and serological incidence of infection. Figure 3 shows the incidence of antibody rises in per cent plotted against age, in relation to a history of influenza during the pandemic. In this figure and

succeeding ones the data for adults are not charted because the very small numbers in certain categories precluded inclusion of this group. The solid line represents those who gave a history of having had the disease and the broken line those who said they had not had influenza. None of these individuals had been vaccinated and therefore antibody rise was a measure of the incidence of infection. Again the high incidence of Asian influenza, averag-

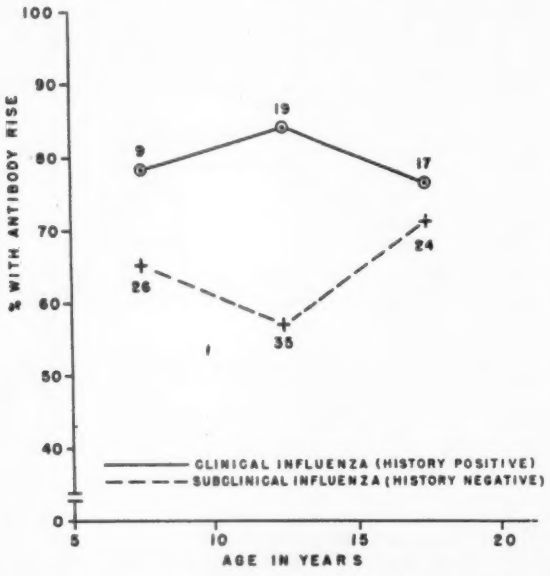

FIG. 3. History of influenza and age-specific rises in Asian influenza antibodies in unvaccinated individuals. Numbers represent total individuals tested in each age group.

ing about 70 per cent, is apparent. Of those who thought they had had the disease, 80 per cent appeared to be right; in sharp contrast to this, of those who thought they had not had Asian influenza, about 64 per cent appeared to be wrong. Thus of a total of 90 unvaccinated individuals who showed an antibody rise only 36 or 40 per cent gave a history of overt disease while 54 or 60 per cent had subclinical or inapparent infections. This is indicative of a very high incidence of subclinical or inapparent infection, but it should be emphasized that the history consisted of the single brief question: Did your child have Asian influenza?—and that this information was not solicited until some 6 or 7 months after the peak of the pandemic had passed. However, the data are in fairly good agreement with those obtained in a

similar study by Carey,[8] in which histories were taken about two months after the disease had reached its peak incidence. The attack rates in his study were similar to those in the present survey in which the clinical attack rate (34.6 per cent), based on a history of influenza, was lower than the actual attack rate (69.2 per cent), as determined by serological study. It is of interest that in most such surveys, where serological tests have been performed, the actual infection rates for influenza have been considerably less than the clinical attack rates, probably because of confusion of influenza with other respiratory diseases occurring at the same time.

Social class and size of family in relation to incidence of rises in antibody. Designation according to lower or upper social class depended upon the individual's status in regard to the six socio-economic areas which have been established for the City of New Haven and which are based upon type of dwelling, occupation, and other factors.[25] Arbitrarily, subjects in areas 1-3 were classified as being in an upper social class and those in areas 4-6 in a lower social class. Figure 4 shows the incidence of antibody rises plotted against age in relation to social class among unvaccinated persons. The solid line denotes those in the lower social class and the broken line those in the upper social class. As in previous figures the numbers indicate the total subjects studied in each group. In unvaccinated individuals the incidence of antibody rises, in general, was slightly higher among those of the upper social class than those of the lower class. However, these differences are not significant and it may be assumed that the age specific attack rates were about the same in both social classes.

On the other hand, in vaccinated subjects, there were such wide variations in the incidence of antibody rises among the different age groups and in the two social classes that no pattern could be discerned. This variability may have been due, in part at least, to a variable response to vaccination rather than to infection, and these data are not presented in detail.

In order to determine whether crowding, as judged by size of family, was significant, the subjects were divided into two groups. One group comprised those individuals with six or more in the family and the other those with families of five or less. Figure 5 shows the incidence of age specific antibody rises in per cent in relation to size of family. The solid line indicates subjects with larger families and the broken line those with smaller families. As was true in the comparison between social classes, antibody rises were about the same in all age groups among unvaccinated individuals, and there was no significant difference in the incidence of rises between subjects with large families and those with small families. Thus, differences in social class and size of family appear to have had little or no influence upon the incidence of Asian influenza in unvaccinated persons of school age.

Comparison of Figures 4 and 5 shows that the curves based on social class are almost identical to those based on size of family, the group with larger families corresponding to lower social class, and that with smaller families corresponding to upper social class. This striking similarity suggested that the upper social class might be composed mostly of smaller families and the lower class of larger families. Analysis of the data indicated that this actually was the case, at least, among unvaccinated subjects. Interestingly enough, however, among vaccinated subjects there was a higher prevalence of larger families in the upper social class.

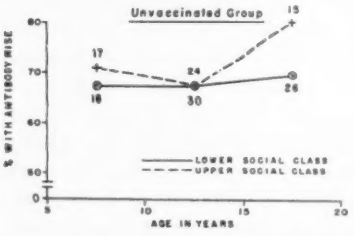

FIG. 4. Social class and age-specific rises in Asian influenza antibodies. Numbers represent total individuals tested in each age group.

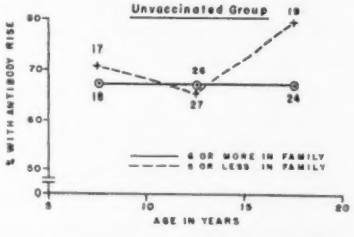

FIG. 5. Size of family and age-specific rises in Asian influenza antibodies. Numbers represent total individuals tested in each age group.

COMMENT

Although a number of careful studies have shown that definite relationships exist between socio-economic status as well as other environmental factors and the age-specific attack rates of some infectious diseases, relatively little information is available concerning such relationships in acute viral infections of the respiratory tract. In diseases, such as the enteroviral infections, which are spread through the intestinal-oral circuit, it seems certain that poor environmental sanitation is at least partly responsible for the higher prevalence among lower socio-economic groups. Thus, antibodies against poliomyelitis reach a peak prevalence at a much earlier age in some parts of the world where poverty is rife and sanitation is at a low level, than in wealthier and more highly developed areas; and, there are some data which suggest that the rate of development of antibodies against both poliomyelitis and streptococci, in the temperate zone, is inversely related to socio-economic status.[1, 9, 10, 18, 19, 26, 35, 39] That lower socio-economic status and crowding are conducive to increased mortality and incidence of rheumatic heart disease is well known.[27, 28]

Perhaps less well documented but nonetheless generally accepted is the premise that crowding results in a higher incidence of the common respiratory illnesses. The Cleveland family studies have clearly demonstrated a higher incidence of respiratory infections in young school children than in those not attending school. Furthermore, in general, the larger the family, the greater were the attack rates for both family and individual. On the other hand, it was felt that there was little, if any, evidence that the incidence of the common respiratory infections was related to economic status.[8] Lim observed lower attack rates of Asian influenza among Europeans than among Asians, although the latter had higher pre-pandemic levels of A and A-prime antibodies. He interpreted these findings as meaning that the differences in susceptibility were not due to differences in previous experience with other strains of influenza virus, but that socio-economic conditions played an important role.[17]

While minor differences in the incidence of antibody rises undoubtedly existed in the present study there was no apparent relationship to socio-economic status and crowding, as judged by size of family; and, it seems probable that these factors played no part in determining the incidence of Asian influenza among unvaccinated subjects.

In addition to the possibility of sampling errors due to the relatively small numbers of sera tested, several other sources of possible error in this study should be considered. Asian influenza may have produced, in some subjects, an antibody response too poor to be detected by the techniques employed. Furthermore, in others an initially high titer of antibody may have dropped to an insignificant level by the time the second serum samples were obtained, several months after infection. Obviously, a rise in antibody in unvaccinated subjects is significant, but failure to demonstrate a rise does not necessarily exclude infection. Thus, some negative results may be misleading and may be indicative of an attack rate lower than that which actually occurred. Unvaccinated subjects showing rises in antibody demonstrable by the complement fixation test alone—a test which is not strain specific—are assumed to have been infected with the Asian strain of virus. Such an assumption seems justified, in view of the fact that the Asian virus was highly prevalent and no other strains are known to have been present at this time. Among vaccinated subjects, of course, there is no way of determining whether the antibody rises were due to infection or to vaccination. Finally, designation as to social class was somewhat arbitrary and was formulated in accordance with data which were based on socio-economic conditions as they existed in New Haven in the early nineteen thirties, with revision in 1950-1951. However, it is thought that significant differences still exist among these six socio-economic categories, although many changes doubtless have occurred.

SUMMARY

A serological survey for Asian influenza antibodies was carried out among a group of 286 inhabitants of New Haven, Connecticut. Paired sera, collected before and after the influenza pandemic of 1957-1958 were tested by both the CF and HI tests. The incidence of antibody rises was 65.0 per cent in unvaccinated and 42.5 per cent in vaccinated individuals. The highest incidence occurred in elementary and high school students; and among unvaccinated subjects subclinical illness accounted for 60 per cent of the total morbidity. HI Asian antibodies were not found in the pre-pandemic sera; CF antibodies were present in many but appeared to afford no protection against Asian influenza. Social class and size of family had no significant effect upon the incidence of antibody rises among unvaccinated subjects.

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SEROLOGICAL EPIDEMIOLOGY IN MEASLES**

One usually thinks of measles as a minor childhood illness through which we all must pass and as a nuisance more than a danger. But this was not always the case. In colonial America, two hundred years ago, measles was dreaded like the plague, and today in remote parts of the world, on isolated islands and in the Arctic, it can be a devastating disease. Even here and now in the United States it causes several hundred deaths each year. In 1957, the last year for which complete data is available, 410 deaths were attributed to measles, a greater number than that caused by poliomyelitis. It is for this reason that we have seized upon the serological tests developed by Enders and Peebles[2] in order to study the epidemiology of measles more fully. Both complement fixation and neutralization tests are available. The two tests give almost identical results and have been used interchangeably.

The first part of this paper deals with studies on the development and persistence of measles antibodies. One of the purposes of these studies was to determine the degree to which measles cases are actually reported in the city of New Haven. It was assumed from the start that the reporting would be far from complete as it has been shown in a study carried out in Hagerstown, Maryland[4] that, even when conditions were unusually favorable, reporting might only account for 40 per cent of the cases actually occurring. A second purpose was to determine whether the pattern of universal susceptibility to a first attack of measles and durable immunity thereafter, which has been observed in epidemics in isolated areas, would also apply in areas where the disease is endemic.

A first step was to determine the normal pattern of antibody development during the disease. The curve in Figure 1 is based on data obtained by Dr. Viggo Bech in a study, carried out at Yale, of 212 serum specimens which he had collected from 71 cases of all ages during the severe measles epidemic in Greenland in 1955.[1] In both this study and an earlier one carried out by Ruckle and Rogers[3] antibodies to the measles virus were always

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absent prior to development of the rash but appeared soon afterwards, in most cases within 48 hours. Peak titers were reached about one week after appearance of the rash and declined only slightly during the next two months.

Knowing that antibodies appear regularly in measles and persist for a considerable period, we next compared their prevalence in different age groups of a normal population with the reported local case attack rate.[3] The

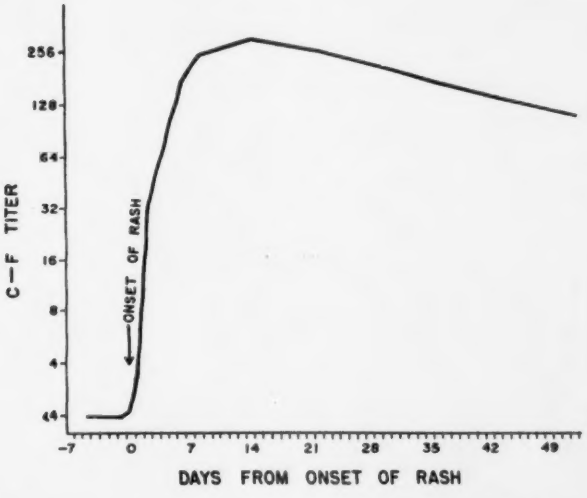

FIG. 1. Development of measles CF antibody. (Adapted from Bech, 1959, ref. 1.)

lowest curve in Figure 2 represents the average annual age specific attack rate in New Haven as calculated from cases reported to the New Haven City Health Department during 1955 to 1958. A marked peak in the attack rate is evident in the primary school age children. The rate falls off rapidly from this peak with increasing age and is negligible beyond high school age. The second curve in Figure 2 is based on the same data and was obtained by summing the attack rate for all years up to the year plotted. If the period 1955-1958 were typical, this curve would give the percentage of the population in each age group that have reported having measles at some time during their lives, and the level at which the curve flattens out in the adult age groups should give the percentage of the population reporting the disease at any time in their lifespan. This final level accounts for 50 per cent of the total population. According to this criterion, half the people in this area

must get through life without measles, experience an inapparent infection, or fail to report their disease. In the light of the Hagerstown study[6] it would seem that failure to report is probably the most important factor.

The third curve of Figure 2 is based on measles neutralizing antibodies in 300 serum specimens from a representative sample of the population in the New Haven area. A high proportion of newborn babies had antibodies,

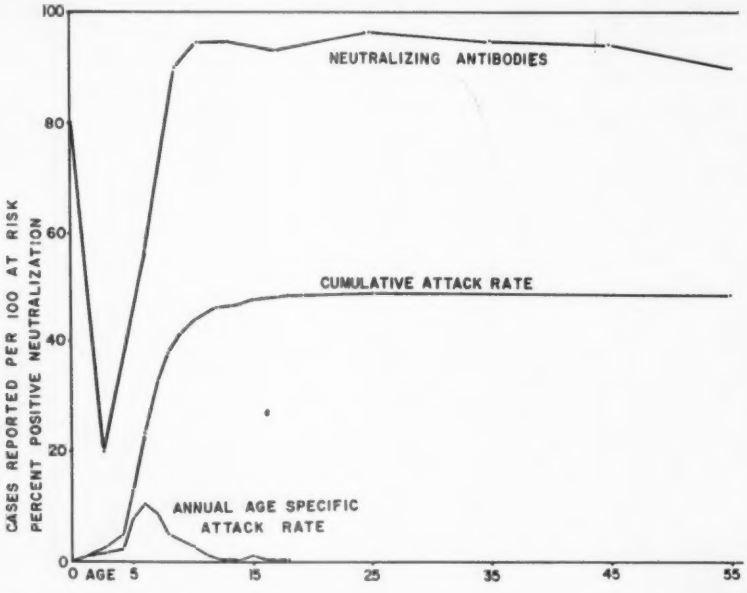

FIG. 2. Correlation between reported measles age specific attack rate and prevalence of neutralizing antibodies in different age groups.

presumably passively acquired. Only 20 per cent of the preschool children had antibodies but even this is somewhat higher than would be anticipated from the reported cases. Perhaps reporting is particularly poor in this group which is not subject to school absentee regulations. Just as in the curve for reported cases, there is a sharp increase in the fraction with antibodies as we progress through the primary school age groups. In the 8-9-year-old group 95 per cent had antibodies. Beyond this age there is little change in the number positive although a slight drop in the average titer has been noted.[8] We know from the reported cases that, without allowance for underreporting, 7 per cent of the population has measles after the tenth

year. Apparently the number in the upper age groups who acquire antibodies through experience with measles is balanced by a similar number in whom antibodies fall to undetectable levels.

A more surprising factor than the lack of increase of the per cent with antibodies in the older age groups is the fact that so few persons lose their

TABLE 1. STABILITY OF NEUTRALIZING ANTIBODY TITERS OVER LONG INTERVALS

No.	*Age at collection of first specimen*	*Initial titer*	*Titers after interval of years*									
			1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
1	6	64	64									
2	17	45	45									
3	17	32	22									
4	21	64	32									
5	25	64	64									
6	25	16	11	16								
7	26	64					64			128		
8	26	32	22									
9	28	64	64									
10	28	64	64									
11	29	11	8									
12	29	45	45									
13	29	32		22								
14	29	60		48	60							
15	30	64					45	64	64		45	
16	31	5	8									
17	32	11							11		11	
18	34	5						5	2			
19	35	8	8									
20	36	22	45									

antibodies in later life. Is this a matter of repeated boosters on re-exposure, or of genuinely steady levels in each individual? It would seem to be the latter. Bech[3] has compared complement-fixing antibody titers in paired sera collected from persons exposed to measles. Samples were obtained at the time of onset of rash in the index case and two weeks later. He found no change in titer in any individual. Similarly, we have compared neutralizing titers of 20 persons in replicate serum specimens drawn a year or more apart (Table 1). Again, there was no significant change whether there was a record of exposure in the interval or not. Some persons had low titers

and some high, but whatever it was, it remained within the limits of reproducibility of the test. Considering all the specimens together there were more decreases in titer than increases but the average for the series gave a decrease of less than two-fold per ten-year interval. This is hardly significant but would fit with the slow drop in average titer that was noted with increasing age in the serum survey.

The data obtained from the antibody survey of the New Haven population have been broken down according to various criteria in order to determine what factors might influence the measles attack rate.[4]

TABLE 2. CONVERSIONS FROM NEGATIVE TO POSITIVE CF ANTIBODY REACTIONS AFTER EXPOSURE TO MEASLES

	Prior antibody status		*Antibody converters*				*Nonconverters*	
	Positive	*Negative*	*Measles*	*Nonspec. illness*	*No illness*	*Total*	*Nonspec. illness*	*No illness*
Gamma globulin*	2	15	1	3	1	5	5	5
No gamma globulin	6	4	0	0	0	0	2	8

* 0.05 cc. per pound 3 days after first exposure and 1 day after rash in index case.

An approximation of the social class of the serum donors was obtained from their addresses by means of the Davie-Myers classification of New Haven residences.[5] The six original classes were considered in two groups with 36 per cent of the total city population in the upper group and 64 per cent in the lower group. In the early age groups the division by this method into social classes was too uneven to permit comparisons but in the 5-9-year-old group, where there were 12 and 29 persons respectively in the upper and lower classes, there was no significant difference either in prevalence or average titer. If any difference existed, one would expect it to be most pronounced in this age group where the rate of antibody acquisition is greatest. No influence of social class could be demonstrated in any of the older age groups. Thus in contrast to poliomyelitis, social class, as we have measured it, has no effect on the prevalence of measles.

On the other hand, there was a distinct correlation between family size and the age at which measles antibodies were acquired, particularly in the preschool age groups. By five years of age 50 per cent of the children in families with three or more children had antibodies, whereas none of the children in smaller families were positive. It may be imagined that in the

larger families the first child to enter school would contract the disease there and in turn infect younger siblings at home, a pattern which is well established in epidemics of acute upper respiratory disease. Where the family is small, there would be less likelihood of its containing a school age child and the preschool children in the home would often be relatively protected from infection. On reaching school age the effect of family size was rapidly eliminated and by 11 years of age completely erased.

Let us turn now from a consideration of populations to look at individual responses (Table 2). An outbreak of measles—it was too limited to be called an epidemic—occurred in a home for retarded children from whom prior serum specimens had been collected. The first child to get measles had been out of the home before becoming sick and returned only two days before onset of the measles rash. Thus the time of initial exposure of the others could be sharply defined. Seventeen children were given an early and moderately large dose of gamma globulin. The gamma globulin had a neutralization titer of 400 and, even if it had all entered the circulation simultaneously, would have given a barely detectable level of antibody in the blood. Fifteen of the children receiving gamma globulin had no prior antibodies but only one of them developed a recognized case of modified measles. Four others, however, developed measles antibodies within nine weeks of first exposure. Three of these had a febrile illness during the month after exposure but none of the illnesses was recognized as measles in spite of close medical supervision. Many other children, including several with prior immunity, had similar nonspecific illnesses in the same period. Thus it appears that measles antibodies and, we may infer, measles immunity may develop in the absence of apparent disease when gamma globulin is used.

There is one other unexpected point in the results presented in Table 2. Four of the children who did not get gamma globulin did not have prior antibodies but none of them developed measles. Now, as has been shown in the survey data, there does seem to be a fraction of a normal population in whom antibodies fall to an undetectable level while immunity persists, but this is less than 10 per cent not 40 per cent. Furthermore, one child not included in this study, but exposed at the same time and under the same conditions, has since contracted measles as the result of another exposure. It would, therefore, seem that the amount of virus circulating in this home was not what would have been expected if six full-blown cases had occurred. The modified and inapparent cases could not have been very contagious, since most children who escaped infection from the index case during the brief period when he was disseminating virus in the home did not become infected by others.

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CONGENITAL MALFORMATIONS:
Environmental Influences that Act to Cause Them

The complacency with which congenital anomalies were once interpreted as expressions of faulty inheritance was rudely shaken in 1940. A convincing demonstration had just occurred in Australia that German measles contracted early in pregnancy by the mother may initiate congenital cataract, deafness, or congenital heart disease in the fetus. A great area for medical exploration had opened. To appreciate the consequences of the discovery, consider the impact on the then current interpretation of congenital cataract—that its presence or absence was determined by genetic factors. Almost without dissent or even questioning, the clinical entity was presumed by physicians to be an inherited defect. For example, in one textbook of wide repute, the occurrence of a single case of congenital cataract in a family of over 40 members was interpreted as indicating a mutation. At the time the book was prepared no one could challenge the inference as unreasonable, but after 1940 anyone had the right to raise the questions: "How do we know that the mother didn't have rubella during pregnancy?" Or, "How do you know that other intercurrent or metabolic illnesses, accidents or operations acting during pregnancy did not cause the defect?"

Since German measles was accurately described as long ago as 1840, it may be profitable to digress just a moment in order to examine why the simple cause and effect relation between maternal infection and congenital defects had not been recognized earlier. The answer, I am sure, lies in the natural behavior of rubella. Ordinarily it is one of the "common communicable diseases of childhood," and relatively few adults are spared to become component parts of the susceptible population. Only half of these would be married at any one time, and less than half of the susceptible married women would be expected to be pregnant. Even of these, only one third would be in the first trimester of pregnancy. Thus, the chances are small for any one physician to see many cases of rubella during early pregnancy in the course of his professional life. Moreover, only 25 per cent of women with first trimester rubella get into trouble; and the risks that

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they run are variable. However, in Australia in 1939 the stage was set for rubella to make the rounds of the young married set in a way that seldom occurs. There had been no major outbreak of rubella in Australia for 17 years before 1939 when Great Britain moved to war. The combination of population movements against a background of three missed cycles of the disease guaranteed the country wide and epidemic spread of rubella when it broke out in 1939 and 1940. Thus an unusually large number of pregnant women were ready to contract the disease, and in fact did so. The result was the crop of babies with rubella defects who were born in 1940 and 1941.[1,2]

Since that time, animal experiments have confirmed and extended the principle. A wide variety of agents — infectious, chemical, endocrine, dietary, radiant, and gaseous—are able to induce congenital defects in birds, fish, and mammals. And as important as the role of the infectious agent is that of the fetal host, for the nature of the defect induced is determined by the stage of gestation at which fetal injury occurs.[3]

What I have just given is the merest bird's eye view of the great expanse of medicine—embryo medicine, the Japanese call it—which has been opened up by scientific advances during the past two decades. For a century before 1940 many brilliant physicians and biologists, St. Hilaire, Dareste, Ballantyne, Mall, Hale, and others, made far-reaching observations and inferences that led them to suspect the operation of environmental factors in the production of congenital anomalies. After 1940 no room was left to doubt that environmental factors do in fact cause the production of many congenital anomalies. We know this as certainly as we know that a family of viruses produce poliomyelitis. And as with poliomyelitis, rickets, or any other disease, the problem is susceptible to approach at three levels—through the clinic, through the laboratory, and in the field by epidemiological methods.

With this introduction I propose now to review some of our scientific knowledge of congenital defects and to give consideration to principles that bear on their etiology and epidemiology. Historically, three of the basic sciences may be said to have furnished most of our knowledge of the developing conceptus. These three include the bedrock discipline of embryology, the study of prenatal pathology or teratology, and thirdly the science of genetics. However, no one, not even the obstetrician, views the baby developing a congenital malformation. The baby is seen by no one until several months have elapsed since a departure from the normal sequences of development first occurs *in utero*. This puts a severe clinical obstacle in the way of anyone trying to construct an epidemiology of congenital defects.

One may start the task by studying first two types of congenital disorder, the one inherited (Fig. 1) and the other acquired (Fig. 2). Both disorders, achondroplasia and mongolism, involve arrested growth of the long bones and floor of the skull so severely that they have in common the end result of dwarfism and brachycephaly. Yet here the resemblance stops, for the mongol is mentally retarded and sluggish, whereas the little court jester (Fig. 3) is bright and agile enough. There is no confounding of the two conditions clinically, or epidemiologically, so different are the congenital stigmas and the attributes of the two kinds of mothers and ancestors further back. To diagnose mongolism in an achondroplastic dwarf would be something of a feat, but not, I think, impossible. The achondroplastic trait runs in families (Fig. 4) and, as far as one can see, it is the human counterpart of the bulldog, Dexter cattle, or Ancon sheep. If human beings were to be bred selectively as animals are, one could doubtless breed strains of these circus dwarfs, even as man has bred the Pekinese, the pug, the bulldog, and the dachshund and other breeds with either a normal or brachycephalic skull riding on top of achondroplastic limbs.

Mongolism, by contrast, does not run in families, nor do mongoloid patients mature and reproduce. Since the condition occurs about once in a thousand births, it defies comprehensible interpretation as a genetic manifestation. Even the long-awaited occurrence of heterozygous twins, both mongoloid, has recently been observed.[7] If mongolism is a mutation, it occurs with an incredible frequency and inexplicable relation to maternal age. For example, the risk of producing a mongoloid child has been observed to increase about 50 or 100 fold from around 0.3 per 1,000 pregnancies in the twenties, to 15 and higher in the forties. This is probably the most striking epidemiological constant that has been unearthed about any of the congenital defects. In these older women, vaginal bleeding during the first trimester of pregnancy appears to be related to the appearance of mongolism in the baby. Presumably, the vaginal bleeding is a manifestation of the same uterine disorder that is to mark the baby for life.

The stigmas of congenital syphilis, of Hutchisonian teeth, deafness, interstitial keratitis, should have alerted physicians to the importance of maternal disease for fetal health a generation ago. In the narrow sense, of course, the relation of maternal to fetal syphilis was well known many years ago. However, an appreciation of congenital syphilis developed too specifically in relation to spirochetal pathology for the broader principles to emerge. The time was not right and it took an epidemic of a supposedly innocuous "childhood disease" to bring the new principle out into the open. Now we are ready to study by epidemiological and statistical methods how

congenital malformations, the pathogenesis of which is hidden from view, may have a relation to minor disease processes and lesser events of medicine as we know about them from hospital visits, office practices, house calls, and minor operations. Family pedigrees and serious diseases are not the only evidence that bears on the causes of malformations with which babies are born. Obstetrical notes and a mother's memory may be quite as illuminating.

To be sure genetic influences are powerful determinants of the child's normal constitution and of some congenital abnormalities. Bulldogs and achondroplastic dwarfs are bred, not induced. On the other hand, there is no evidence that human beings breed cyclopia, conjoined twins, tracheo-esophageal fistula, mongolism, ectromelia, Hutchisonian teeth, cerebral palsy or Erb's palsy, although some mothers and some fetuses are more susceptible than others to environmental adversities that probably cause such defects.

Some idea of the principles underlying the genesis of acquired malformations in animals is gained from systematic study of pregnant mice by administering a single, standardized, and controllable injury on different days of pregnancy. In addition to demonstrating that hypoxia of the fetus or embryo is a potent teratogenic agent, the experiment reveals that both degree and timing of maternal stress in pregnancy are also of decisive importance. Pregnancy in the mouse is usually a matter of 19-20 days' duration.

Within a low pressure chamber pregnant mice are exposed to hypoxic atmospheres equivalent to the 25,000-28,000 feet found near the top of Mount Everest for a period of five hours on the various days of pregnancy. Delivering of the young is by section on the 19th day in order to prevent the mother from devouring defective fetuses. In this way, the entire contents of the uterus are examined for results of intra-uterine anoxia as manifested by gross congenital defects. Control studies are also made.

Under these conditions a whole spectrum of prenatally dead and defective fetuses is obtained, which would correspond to the continuum of reproductive wastage to be observed among human beings. Although the counterpart of mongolism and mental retardation could hardly be recognized in the mouse, many different types of recognizable defect are observed, varying from gross monstrosities to minor defects. Some form of anencephaly is found in nearly a third of litters after significant anoxia on about the 8th day of development, a period that is also critical for defects of the axial skeleton. Cleft palate occurs after hypoxia administered on the 14th day; and so-called "open eye" from fetal oxygen deprivation occurred on the 16th day of gestation.[4]

FIG. 1. Mother and child, both with achondroplasia.

FIG. 2. Mongolism at birth.

FIG. 3. Don Carlos and his achondroplastic dwarf, by Velasquez.

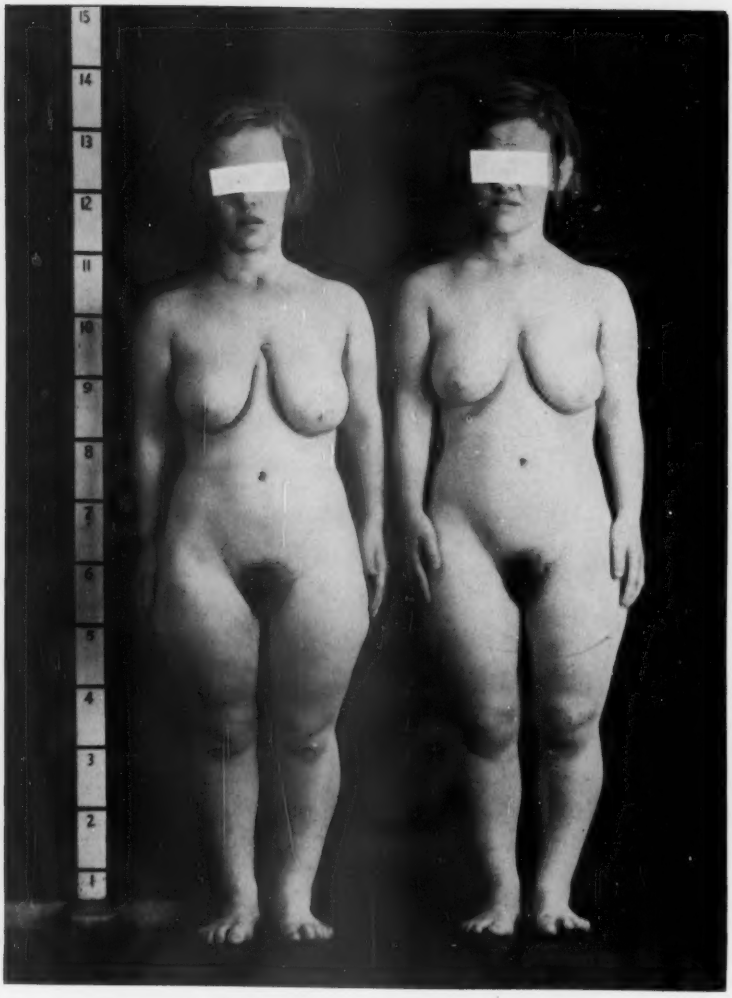

FIG. 4. Identical twins with achondroplasia.

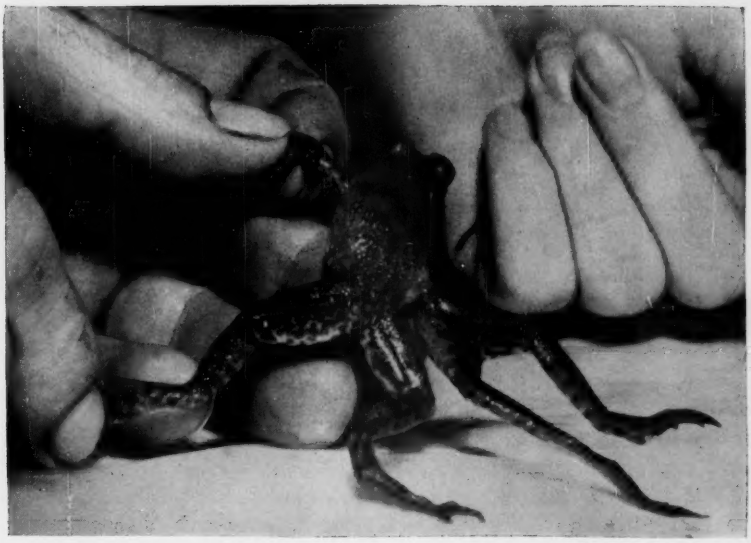

FIG. 5. A six-legged frog found near Tunica, Mississippi, September, 1958 (McClurkin, J. I.[a]).

The validity of applying the principles gained from the study of the anomalies of rodents to the interpretation of human anomalies would seem as sound as to study viruses in roller tube cultures. Moreover, the German measles story alone indicates the importance of timing of a fetal stress in human beings. The time of infection was even more important than the kind of infection in deciding the result. Thus, congenital cataract was a result of rubella at the fifth week of pregnancy, congenital heart disease at the sixth and seventh, and deafness at around the eighth week. So too with other human anomalies such as tracheo-esophageal fistula, cleft palate, and mongolism, which give every suggestion of being naturally related as individual members of a series of developmental arrests. The single patient with anomalies is only an isolated unit of a larger dynamic process, or like the single case of congenital syphilis.[8]

Enough knowledge of the experimental epidemiology of congenital anomalies in animals has been gathered[6] so that a recent glimpse of their spontaneous occurrence in Tunica, Mississippi may be revealing. Some of those who attended the annual meeting of the American Public Health Association in St. Louis last fall may have noticed an item in the *St. Louis Post Dispatch* on the epidemic occurrence of six-legged frogs in a Mississippi lake during the past summer. According to the manager of the farm which abutted the lake, these freaks (Fig. 5) were seen earlier in the fall "by the hundreds." Of course, it would have been more informative if he had made an accurate survey of the frog population of the lake during the different months of 1958. However, such evidence as we have indicates that there was in fact an epidemic of six-legged frogs near Tunica, Mississippi in September and October 1958, and that a significant percentage of the eggs hatching out that summer contained conjoined twin embryos. I would expect that percentage-wise these abnormal specimens would be handicapped greatly in eluding natural enemies. Thus one is hardly surprised that Professor McClurkin of Memphis State University in late October 1958 could find only one abnormal specimen after an hour's search and estimates that, all told, about 150 specimens were actually captured by several collectors.[9]

What we would like to know epidemiologically and ecologically is whether some environmental upset occurred during the early stages of embryonic development, or during metamorphosis from the tadpole. Actually, an eight-year study of temperatures for February near Tunica indicates clearly that February 1958 was extremely cold, with the mean recorded as 34.9° F. The mean February temperature for the preceding seven years averaged 47.5° F. It seems possible that the epidemic

of six-legged frogs was related to this environmental disturbance during a critical period of metamorphosis. The event is being studied further and in relation to possible contamination of the frog pond by nursery sprays.

To turn from frogs and mice back to human beings, the main difficulty to be encountered in establishing an epidemiology of congenital anomalies is that diverse causes, anoxia, maternal rubella, and presumably other virus infections, are probably capable of initiating the same kind of defect in the conceptus. Conversely, a single teratogenic agent can induce a whole host of seemingly unrelated handicaps in the conceptus. Rubella, for example, may induce mental retardation, cataract, congenital heart disease, or deafness, to mention only four of its possible sequelae; and the resulting anomaly is a function of the stage of development at which the infection occurred.

The critical period determining some of these malformations has been identified: congenital cataract developed after rubella around the fifth week of pregnancy, cardiac malformation from the sixth to the ninth weeks of embryonic life, and congenital deafness at about the ninth week. On the other hand, the critical period for many other malformations—cyclopia, conjoined twins, ectromelia and tracheoesophageal fistula, for example—has to be inferred. One does not have to be too diffident about making these inferences, however, for three of the four can be produced in the laboratory during very early stages of embryonic development. Even the six-legged frogs help us to understand human freaks.

In summary, when I talk today on the epidemiology of congenital defects, I cannot close in on my topic with the same directness that was shown by you who spoke this morning. One has to take into consideration altogether too many viruses, too many stresses, too many weeks of pregnancy, and too many defects to expect to systematize the variables in 1959. However, the occasional importance of an acute triggering process has been firmly established by the German measles story and the aftermath of the Hiroshima bombing, a chapter which I have not had time to explore here. Whether a suspected maternal stress be acute or chronic, infectious or noninfectious, the epidemiological challenge is still ahead. It is to measure the diverse impact on the conceptus of stressful agents in relation to any deviations of growth and development that may result, and in relation to the time when the suspect stress is acting.

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ABO BLOOD GROUPS AND CANCER OF THE STOMACH

In 1953 Aird *et al.*[1] reported data which showed that the incidence of carcinoma of the stomach is higher in those subjects who belong to blood group A than in those of blood group O. This paper provided a stimulus for several investigations, and by 1959 Lavenhar in a review[4] was able to list results from 12 different centers. These showed that the mean incidence of cancer of the stomach was 21 per cent higher in group A than in group O; the data therefore provide general confirmation of the findings of Aird *et al.* In one center with 1,146 cases, however, no difference between the two incidence rates was found, and in two other centers the difference was small and insignificant. In these circumstances it is worthwhile to investigate a suggestion first made by Jennings *et al.*[6] that the relationship between blood group and carcinoma of the stomach might vary according to the site of the lesion within the stomach. The present interim report is based on the first half of the data we are collecting in order to test this hypothesis.

MATERIALS AND METHODS

The analysis covers 707 cases of gastric carcinoma registered at the Division of Cancer and Other Chronic Diseases, Connecticut State Department of Health, during the period 1950 to 1953. An additional 439 cases registered during this period were omitted from the final analysis because information about blood group or site of lesion was not available.

Hospital records on each patient were consulted to obtain data on the site of the lesion. In 37 per cent of the cases the site was obtained from the pathologist's report, and in the remainder the decision was based on the findings at operation or at radiographic examination. Using the criteria of Billington,[2] we classified the site of the lesion as: (a) pylorus and antrum, (b) body and fundus, and (c) cardia. In 48 cases the involvement was so extensive that the site could not be specified.

Data on the age and sex of each patient were available at the Cancer Registry. The ABO blood group had previously been obtained by Eisenberg *et al.* in the course of an earlier investigation[3] on the same subjects.

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RESULTS

In Table 1 are the findings on the relationship between the site of cancer, the sex of the subject, and blood groups A and O. The results for blood groups B and AB are not included in this preliminary report, since the number of cases in these two groups is small, and neither this nor any previous investigation has led to any hypothesis relating these groups to carcinoma of the stomach.

The main point of interest is the relative frequency of blood groups A and O. In the total series studied there are 308 subjects belonging to

TABLE 1. SITE OF GASTRIC CANCER BY SEX AND BLOOD GROUPS A AND O

Site	*Males*			*Females*			*Total*		
	A	*O*	*A+O*	*A*	*O*	*A+O*	*A*	*O*	*A+O*
Pylorus and antrum	95	63	158	45	41	86	140	104	244
Cardia	21	20	41	18	8	26	39	28	67
Body and fundus	82	80	162	35	36	71	117	116	233
Extensive	9	19	28	3	9	12	12	28	40
Total	207	182	389	101	94	195	308	276	584

group A and 276 belonging to group O. It may be noted that in the general population O is more frequent than A. The analysis of the over-all ratio A:O is given in the paper by Eisenberg *et al.*[8]

In males, the ratio A:O is high for the pyloric group. If this group is compared with the remaining three, the difference is significant ($x^2_{(1)} = 4.65$; $P < 0.05$). In females the ratio is 1.1 for the pyloric group, which is about the same as the corresponding ratio for the total female cases. The ratio A:O is high for the female cardiac group but the number of cases involved is small.

Certain other findings may be referred to briefly. An analysis has been made of the data classified by site, by blood group, and according to whether the site of cancer was determined by the pathologist or otherwise; the method of diagnosis of site did not affect the relationship between blood group and site. Similarly, the fact that a subject was Italian, Polish, or other nationality did not influence the relationship between blood group and site.

DISCUSSION

Eisenberg *et al.*[8] compared the distribution of blood groups in the present series of cases with the distribution in a set of controls and found that group A was relatively more common in the patients and group O in the controls. From the results discussed above, it appears that the excess of group A in cancer patients is found mainly in male subjects with cancer of the pyloric region, and possibly in female subjects with cancer of the cardia. Three other workers have published data on this problem; their results and those of the present study are presented in Table 2.

TABLE 2. BLOOD GROUPS OF PATIENTS WITH GASTRIC CANCER ACCORDING TO SITE

	Frequency of site and blood group					
	Pylorus		*Body*		*Cardia*	
Author	*A*	*O*	*A*	*O*	*A*	*O*
Jennings *et al.*	42	20	18	23	10	6
Haddock *et al.*	87	118	*	*	*	*
Billington	96	53	47	154	50	24
White and Eisenberg	140	104	117	116	39	28

* Body and cardia combined: 109 A and 85 O.

In three of the four investigations there is an excess of group A in subjects with pyloric cancer and no such excess in cancer of the body of the stomach. This finding, however, is by no means securely established. One major difficulty is the exclusion of cases on whom information about blood group and site is not available. Another problem is that we are testing for relatively small differences in the presence of various sources of heterogeneity. In the present investigation it appears that the results vary somewhat according to sex. We have also noted some heterogeneity associated with age and with place of residence, these in turn probably being related to nationality. In none of the work so far reported have the cases been sufficient to control these various factors simultaneously.

All the data now available show that group A is more common than group O in cancer of the cardiac portion of the stomach. Even the pooled data, however, are inadequate for a definitive opinion on this point.

The findings in regard to cancer of the body of the stomach are contradictory. Billington reported such a large preponderance of group O that, in

his total material, the ratio A :O was not higher than the ratio in the general population. The present investigation does not support this finding.

The main interest in these investigations is the study of the relationship between blood groups and cancers of different portions of the stomach. The finding of a relationship with parts of the stomach, however, also throws light on the older problem of a relationship with the stomach as a whole. It is difficult to attack this latter problem by a retrospective investigation in a country such as the United States, because of the question of what constitutes a proper control group. One possible solution is a follow-up study, but until this is arranged, some information can be gained without the use of external controls by comparing the blood group distribution of patients having pyloric cancers with the distribution in patients having cancer of the body of the stomach.

SUMMARY

1. A series of 707 cases of gastric carcinoma was classified according to blood group, site of cancer, age, sex, and place of residence.

2. In the series as a whole, blood group A was commoner than blood group O, and the excess was most marked in males with cancer of the pyloric region.

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DE MOTU LOCALI ANIMALIUM. By William Harvey. Edited, translated, and introduced by Gweneth Whitteridge. Cambridge, University Press, 1959. xii, 163 pp. $10.50.

The bright light of William Harvey's discovery of the nature of the blood's circulation usually outshines his other contributions, notably the important studies on the embryology of the chick and the deer. However, the *Exercitationes de generatione animalium* at least was published (1651). Now Dr. Whitteridge, at the invitation of the Royal College of Physicians, has made accessible a virtually unknown, previously unpublished, and exciting series of notes by the great physiologist, his *Of local movement in animals*.

It appears that Harvey planned a treatise on the movement of muscles even while he was preparing the *De motu cordis*. Anything that he might have written on muscles was thought to have been lost until his notes were discovered in the British Museum in 1847. The notes, mostly in Latin, are handwritten and nearly illegible except to the specialist, as is evident from the facsimile reproduction of a page which serves as frontipiece in Mrs. Whitteridge's book. Her difficult task, which she has completed with great skill and scholarship, was to decipher the notes, to translate their Latin, to supplement the translation with explanatory phrases, and to annotate, edit, and integrate the whole. The thoroughness which the editor, Archivist of St. Bartholomew's Hospital (where Harvey was once a member of the staff), has devoted to her work has extended to examination of the original by ultraviolet light in search of undiscovered text (there was none), dating of the paper through the water mark, and reading the books which Harvey read and on which he comments. Latin and English versions face each other from opposite pages. There is a foreword by Sir Russell Brain, an introduction by the editor, and a bibliography, appendix, and index.

Harvey's notes first recount Aristotle's ideas about movement in animals —why it is necessary, the different kinds of movement in terms of direction, motion on land, in the water, and in the air, the varieties of bodily movement, the control of movement by higher centers, and the anatomical structures involved. There is a review of classical opinion as to which elements—nerve, flesh, ligament, or tendon—are actually responsible for movement. Then Harvey presents and supports his own views, still in the outline form which was to be the basis of his book. They are based largely on painstaking observation rather than on experimentation. He was, of course, handicapped by the seventeenth century's lack of histological knowledge, as Brain points out in his Introduction. When necessary, Harvey did not hesitate to speculate. The final chapter includes an interesting series of analogies, for example, "Is the brain the general? The nerves carry the commands, sergeant major. The spinal medulla the lieutenant-cornet. The branches of the nerves which give the signal to the muscles, the captains. The muscles, the soldiers."

It is a pity that Harvey did not write his book.

THOMAS R. FORBES

TEXTBOOK OF COMPARATIVE HISTOLOGY. By Warren Andrew. New York, Oxford University Press, 1959. 652 pp., 220 figs., 4 plates. $15.00.

Dr. Warren's scope is as broad as the animal kingdom, his viewpoint that of the histologist, his intended audience all who are interested in the comparative aspects of animal form and function considered at the cellular level.

At a time when newer techniques are daily adding to the bewildering array of facts concerning cells and tissues there is a danger that even professional histologists may become so fascinated with minutiae that they forget the broad principles on which their science rests. This text undertakes the impressive task of illustrating histological principles by a judicious distillation of facts garnered from the invertebrates and the vertebrates. The task is accomplished expertly, and the army of facts that crowd the book is properly marshalled in support of basic principles. It is no small bonus that Dr. Andrew has written with zest and imagination.

While the approach is comparative, the organization of the text is systematic. After introducing the animal cell and animal tissues, the text treats each of the organ systems in turn. In each case careful attention has been given to the cellular and tissue modifications that reflect the ways in which different species have solved the same problems. In turn attention is given to: skeleton, integument, digestive apparatus, circulatory systems, respiratory organs, reproductive systems, endocrine glands, nervous system, sense organs and tissues producing light and electricity. A final chapter relates the principles derived from comparative histology to broader biological concepts and theories.

Inevitably an occasional term is introduced without prior definition, but on the whole the work is excellently organized and eminently usable. Key references and an exhaustive index enhance the value of this text. The numerous drawings and photographic halftones, which include four plates in color, have been carefully selected for quality and pertinence.

It is a pleasure to recommend a book which fills a real need and which is both accurate in its great detail and a polished literary work that is a pleasure to read.

ALFRED J. COULOMBRE

INTRODUCTION TO HUMAN ANATOMY. By Carl C. Francis. St. Louis, C. V. Mosby Co., 1959. 548 pp. $5.75.

This textbook is an attempt by the author to present the essential facts of human anatomy in the smallest possible compass. He has succeeded, for I doubt if the subject matter could be more concisely stated without being quite incomplete. The book is clearly written, accurate, and well illustrated. It would serve as a good textbook for human anatomy courses at the undergraduate level, including those for nurses. At the end of the book there is a glossary of anatomical terms and review questions at the end of each chapter to aid a student studying human anatomy for the first time to better understand the material presented. In the description of structures the inclusion

of function and medical applications makes the book quite dynamic. I have found such a textbook as this helpful as preliminary reading for medical students who were nonscience majors as undergraduates to enable them more adequately to cope with the massive amount of anatomical data they are expected to learn in their gross anatomy course.

Although the author often includes alternate terms when describing structures, it is unfortunate that the Basle Nomina Anatomica (B.N.A.) (1865) terminology is used as the official source of terms throughout the book. It would be quite desirable for authors of any new books and new editions of books on human anatomy, at any level, to use exclusively the revised terminology approved by the Sixth International Congress of Anatomists in Paris, 1955, as the official source of terms in order eventually to do away with the confusing use of more than one term for each anatomical structure.

E. S. CRELIN

MEDICAL BIOLOGY AND ETRUSCAN ORIGINS. Ciba Foundation Symposium. G. E. W. Wolstenholme and C. M. O'Connor, Eds. Boston, Little, Brown & Co., 1959. 255 pp. $9.50.

To denote the 50th volume in the Ciba Foundation Symposia, the editors at the instigation of Professor F. G. Young of Cambridge have selected a field of study outside their usual purlieus. In a period that is committed to the "multi-disciplinary approach" this volume stands out proudly as a fruitful attempt to reconcile the various approaches of archaeology, physical and social anthropology, classical history, philology, human genetics, and contemporary advances in hematology as applied to the elusive questions of the ethnology of the Etruscans. It is always refreshing to read how some one in another field of study goes about solving his problems, what stumbling blocks he encounters, what hypotheses have been advanced in the past, then modified, then re-evaluated in the light of new evidence, etc., what new tentative hypotheses can be advanced, and, most important, what riddles remain unsolved.

The volume contains an introduction by R. M. Cook of the Museum of Classical Archaeology at Cambridge which delineates the problem, setting it against the broad context of the disciplines involved. This is followed by 16 original contributions chiefly by English and Italian scientists. Most informative are the well-illustrated archaeological article by Hugh Hencken of the Peabody Museum at Harvard and the general article on the contributions of various scientific disciplines by Neppi Modena of Genoa. Articles on blood grouping as a tool in genetics and the relevant hematological data are supplied by Mourant, Cepellini, Morganti, Siniscalco *et al.*, and Harris *et al.* The diverse perspectives upon the central problem are brought into sharper focus by the group discussions. The volume is arranged, illustrated, printed, edited, and planned in the fine style we have accustomed ourselves to associate with publications from this quarter.

In a very real sense museums can be the sepulchres of cultures whose survival civilization has rendered impossible. Most of us know little about the

Etruscans and care less. Apparently, the loss is ours, for this volume makes it plain that Etruscan culture was rich and vital and that its careful study is a pursuit with endless fascination, innumerable mysteries, and considerable scientific importance. In a world beset by insoluble problems and torn by unresolved conflicts there is a great deal to be said for scholarship for its own sake, and the Ciba Foundation merits our thanks for permitting it to be said.

WILLIAM B. OBER

PERSONALITY PATTERNS OF PSYCHIATRISTS. A STUDY OF METHODS FOR SELECTING RESIDENTS, Vol. 1. By R. Holt and L. Luborsky. New York, Basic Books, 1958. 386 pp. $7.50.

Holt and Luborsky's prodigious two-volume report is the outcome of a systematic ten-year effort to learn what personal qualities a physician should have who wishes to enter residency training in psychotherapeutically oriented psychiatry. In following the objective of assessing applicants for psychiatric training and predicting their future competence, the authors, both psychologists at the Menninger Foundation at the time of the investigation, evaluated the interviews and battery of psychological tests and other credentials as well as subsequent ratings from supervisors and peers and follow-up data. The immenseness of the task is best illustrated by the fact that the writers felt it important to publish in addition to volume one, the main text, a second volume containing footnotes, tables, and more detailed data on a number of issues not presented in the text. This unquestionably results in a smoother presentation and for those readers not specifically interested in the more itemized, technical aspects of the research, volume two will not contribute greatly. The book (which will henceforth refer to volume one) is composed of four major sections. The first is devoted to the background of the study, some historical aspects of psychiatry in general and the Menninger School in particular, and an overview of the sociological, economic, intellectual, and religious make-up of the group investigated as well as their future professional expectations. The subjects of the research, spread over six classes at Menninger's, came from urban, middle class families in which the percentage of parental divorce and separation was considerably higher (10 per cent) than for the population at large. Their average IQ of 128 falls in the very superior category, with individual scores ranging from 110 to 145.

Part II, by far the largest section, dealing with the theoretical and methodological issues as well as the findings, is a more uneven presentation than the other parts of the book. In the attempt to offer this section in the most readable form the authors have compromised on parsimony becoming at times rambling and cumbersome in the service of clarifying experimental and statistical considerations with which some readers might be unfamiliar. A major issue central to the investigation is that of deciding which factors in the personality of the applicants will differentiate between good and poor residents and later psychiatrists, and even more important, what criteria to

apply in order to evaluate these predictions. It is a particularly great problem in psychotherapeutically oriented psychiatry where treatment outcome cannot be easily measured and where intellectual, interpersonal, and technical adequacy of the therapist are difficult to judge in an objective manner. The principle criteria decided upon were ratings based on general observation of routine work that were made by supervisors and peers. A secondary string of criteria included completion of the three-year residency, entrance into psychiatric practice, and board certification. The results are rather disappointing. Correlations hover in the '20's, occasionally going higher, but frequently also dropping to near zero.

These findings are not due to poor workmanship, for throughout the book one is struck with the thoroughness of the study, the excellence not only of the authors but of the cooperating staff, and the heavy demands made upon the candidates and residents through multiple interviews and a large battery of psychological tests. Freud's story about a medieval king who had an infallible way of telling whether or not the person was a witch (boil suspect in cauldron for three hours, whereupon the taste of the broth is a sure sign) is really not a correct statement of either the intent of the researchers or the ordeal of the psychiatric residents undergoing evaluation for *Personality patterns of psychiatrists—a study of methods for selecting residents.*

CARL N. ZIMET

EMERGENCY WAR SURGERY. U.S. Armed Forces issue of NATO Handbook prepared for use by medical services of NATO nations. Washington, D. C., U.S. Government Printing Office, 1958. 411 pp. $2.25.

This handbook was developed by a committee of three surgical consultants representing the military medical services of France, the United Kingdom, and the United States. The names of these consultants are not given. Its purpose is to provide in one easily carried volume a source of information on the care of wounds in war time, "to assure that the best possible medical care would be provided for every member of the Allied fighting forces whenever and wherever he became a medical responsibility because of injury." The handbook limits its coverage to emergency care through the first echelons, battalion aid station, clearing station and field or evacuation hospital.

The book is made up of four major parts with a total of thirty chapters. Part I consists of a general consideration of the various types of wounds; missile, thermal, cold, etc., and a section on radiation injury is included. Methods of treatment of each are concisely presented. In Part II, the three chapters consider the overall responses of the body to wounding, shock, metabolic disturbances, and infection. Remedial measures directed toward these problems are presented. Part III covers general principles of wound management, plus a consideration of injuries to the various body *systems,* vascular, bones and joints, etc. In Part IV, wounds are considered from a *regional* viewpoint, thus completing in an orderly fashion the coverage of trauma. There is appreciable space devoted to the military aspects of patient

care and evacuation. In addition, all of the chapters include material on the handling of mass casualties.

This is a most useful and authoritative little book, which brings together current concepts in the care of the many forms of trauma seen in war time. To have access to such a handbook would be of great value to a physician faced with the problems of care of the wounded. It should be required reading for new medical officers. Even the experienced surgeon would find the book of value as a reference source for information on uncommon types of injury.

Although the orientation is primarily military, the physician in civilian life would profit from the availability of such a large amount of authoritative information in such a compact form. The material is well presented, neatly organized, and carefully indexed. The authors, whoever they may be, are to be commended for taking on a difficult task and producing such an excellent book.

DONALD P. SHEDD

CONCEPTUAL AND METHODOLOGICAL PROBLEMS IN PSYCHOANALYSIS. Leopold Bellak, Ed. Annals of the New York Academy of Sciences, vol. 76, art. 4, pp. 971-1134. New York, 1959. $2.75.

If you have been worrying because you are not entirely clear on the meaning of object cathexis, the relationship between "ego" and "self," or just what is the difference between preconscious and unconscious functioning, you can rest easier because, as this monograph demonstrates, you are in distinguished company. This is a verbatim report of five papers, and much of the subsequent discussion, presented at the New York Academy of Sciences in March, 1958. The reason for the conference was, in the words of Leopold Bellak, the chairman, "Psychoanalysis has as yet spent little time considering its concepts in the orderly, systematic, and experimental way of science." Semantic confusion, which is a major preoccupation of this conference, results at least in part, he feels, from the fact that in the training of psychoanalysts "preceptorship takes the place of systematic teaching." Martha Wolfenstein elaborates incisively on this and points out the dangerously ambiguous connotational aura which "concepts" can take on, lending them a spurious appearance of meaningfulness. For psychoanalysts in training, technical terms are not always precisely defined; they assume a familiarity through repetition, and "induce a sentiment of comprehension and mastery." The (quite legitimate) anxiety aroused when the trainee is confronted with the task of comprehending complex and difficult areas of human experience can be allayed by the seeming order and control that concepts can lend. Finally, she wonders if latent resistance to psychoanalysis and analytic theory—probably present to some degree in most analysts—might not, through reaction formation, lead to dogmatic support of hazy concepts.

It would of course be inaccurate to leave the impression here that all psychoanalytic theory is muddle and semantic confusion; this conference has emphasized these difficulties as an expression of the best kind of critical self-

examination, rather than focussing on the larger and more familiar areas of agreement. The prospective reader should be warned that the monograph is no layman's primer of psychoanalytic thought, but, on the contrary, it presupposes considerable sophistication in basic analytic theory and goes into some of the more recent (and complex) thinking about important problems of revision and addition to "traditional" (i.e., Freudian) theory. Since this cannot be summarized, I will only suggest a few of the areas of concern, and some of the new thinking expressed.

Three of the five papers are concerned with "A critical analysis of some aspects of libido theory"; the first, by Thomas Szasz, is on the concepts of libidinal zones, aims, and modes of gratification; the next, by Alfred Stanton, on problems of object choice; and the third is a discussion by Eugene Pumpian-Mindlin of the energetic-economic aspects of libido theory. The remaining two papers are Bellak's on the unconscious, and Mortimer Ostow's scholarly review of theory of the structural model (i.e., id, ego, and super-ego.) The underlying theme of these papers, and of most of the discussion, is a concern with essentially philosophical problems of scientific method—questions of logic, semantics, epistomology, conceptual models, and definitions. For example, Freud's *original* formulations of libido and instinct theory are shown to have their basis in physical and chemical realms; his conception of psychic energy and its operation is an "hydrostatic" model; and it is a "closed system" (to which the second law of thermodynamics applies.) The latter is said to be the logical basis for the (now questionable) death instinct hypothesis. While there is general agreement that these early Freudian views have evolved and changed, there is concern with the extent to which they still influence and limit our thinking. Several participants, and particularly Pumpian-Mindlin, make comparisons with modern developments in mathematics and physics, where attention has shifted from a focus on *energy* as all-important, to information theory, problems of entropy, and field theory. He recommends that we view psychological functioning as an open energy system, and that field and information theory can be usefully applied. The recent development of ego psychology (a major contemporary focus) and interest in counter-transference are cited as two results of the trend in this direction.

Philosophical problems of operationalism and determinism draw considerable attention, the former because of a widespread contemporary tendency to insist that theory be operationally definable. While they hold this in general to be admirable, there is question whether this can always legitimately be expected, and, specifically, libido theory as it now stands is said not to be amenable to operational definition. Bellak states that determinism has been the largely unchallenged basis of the theory of the unconscious, and he spells out how probability theory would be a more useful construct. Criticism is also directed at the "reductionist" view that it is either desirable or possible to reduce psychological problems one day to the "more basic" physiological and neurophysiological framework.

There are of course many propositions with more psychological than philosophical content. Szasz, for instance, questions at length Freud's as-

sumption that libido is basically pleasure-seeking, and proposes instead Fairbairn's view that it seeks contact with objects: for example, the infant's mouth becomes erotized because it is the route toward, or the bodily structure for, contacting the libidinally desired object (the breast). Stanton, in discussing object choice, would add knowledge of social and group behavior theory to the traditional conceptions of object choice (which see it as an expression of identification, anaclitic relationship, or libidinal satisfaction); he points out that current theory is not very helpful in understanding the object relationships in the mature mutuality of love.

Few of the thoughts reported here pass unchallenged in this symposium, and there are spirited disagreements if not diametrically opposed points of view reported, all of which makes not only interesting reading but lends conviction to the premise of the conference that there is still unresolved difference of interpretation and inadequacy of definition in many of the important constructs of psychoanalytic theory. For the reader with adequate background, it makes stimulating reading.

EDWIN C. SEVERINGHAUS

REPRODUCTION AND INFERTILITY III SYMPOSIUM. F. X. Gassner, Ed. New York, Pergamon Press Inc., 1959. 273 pp. $6.50.

Reproduction and Infertility III Symposium represents the edited proceedings of the third in a series of biennial symposia sponsored by various colleges of veterinary medicine. This nicely organized composite of facts on reproductive physiology is divided into five sections: diseases of reproduction in the male and female, ovarian physiology, steroid physiology and therapy, general problems of reproduction, and semen metabolism. Discussions of the twenty formal papers covering these broad areas as well as a round table seminar on artificial insemination and frozen semen are included, edited by F. X. Gassner. Dr. Gassner, who is well known for his numerous contributions in the field of animal reproduction, was assisted by two other members of the faculty of Colorado State University, R. Jensen and H. J. Hill. Except for two papers dealing with human subjects, the emphasis is entirely on animal husbandry. The paper by Nowakowski on human male hypogonadism is particularly noteworthy. Though much of the subject matter has no direct application to the human, many of the more basic concepts, particularly in the field of ovarian physiology and sperm metabolism, may serve as a guide for studies along similar lines on human material. For this reason, the symposium, which is certainly of value to those interested in animal husbandry, should be useful to workers in human reproductive physiology as well.

LUIGI MASTROIANNI, JR.

MODERN SCIENCE AND THE HUMAN FERTILITY PROBLEM. By Richard L. Meier. New York, John Wiley & Sons, Inc., 1959. xiii, 263 pp. $5.95.

The author starts with the premise that population growth is the greatest single deterrent, with the exception of war, to economic development in the

poorer areas of the world. This is his justification for his examination of the "new scientific possibilities" in the control of human fertility.

This book is divided into eight chapters: (1) The new population problem, (2) analysis of social consequences of scientific development, (3) the human problem of microcosm, (4) fertility changes and developmental planning, (5) the potential breakthrough in fertility control, (6) the prospective spread of the innovation, (7) concerning equilibrium in human population, and (8) the unfinished tasks. A section entitled Appendixes follows that is comprised of four parts: (a) survey of studies relating to vulnerable points in the reproductive process (by Warren O. Nelson), (b) oral control of contraception (by Nathan Millman and Carl G. Hartman,) (c) considerations from the future, and (d) notes on recent research developments related to oral contraception.

This book will interest both nonmedical and medical readers alike. The book is timely, especially with the inclusion of the first two sections in the Appendix. Dr. Nelson has summarized the vulnerable points in reproduction, and Drs. Millman and Hartman have surveyed the contemporary literature on the means of oral control of conception.

In the final analysis, Meier points up the status of our knowledge on fertility control. No convincing quantitative evidence reveals a single oral contraceptive that is 100 per cent effective to this date. Those that are being used can only be used at the patient's risk. There are no long-range studies on the effects of the oral contraceptives on the entire endocrine background. Also, there are no guarantees that these agents work 100 per cent of the time. Finally, what are the side-effects? In the light of the recently publicized and reported warnings that these tablets may prove too dangerous for general use, one must use extreme caution. For as Tyler and Olson reported in Los Angeles there were 22 pregnancies in 3,082 woman months of exposure—an effectiveness about the same as for other contraceptives.

The author is factual in his reporting, but oftentimes his wordy evaluation of the scientist in his culture outweighs the task to which he assigned himself.

JOSEPH THOMAS VELARDO

THE UTERUS. By Joseph T. Velardo and others. Annals of the New York Academy of Sciences, vol. 75, art. 2, pp. 385-1040. New York, 1959. $7.00.

This book contains the transactions of a conference held by the New York Academy of Science in February 1958. As expressed in its introduction, this meeting was meant to bring together the work of the specialists in this area of physiology of reproduction, to summarize the progress of knowledge of the past 20 years and evaluate our present concepts.

One glance at the table of contents is enough to convince one of the tremendous effort that is being made today in all related sciences to bring more light into a chapter of physiology that has remained largely in the hands of the clinician. The histochemists, the biochemists, the physiologists, the biophysicists, the anatomists present their recent contributions. Their meth-

odology is up-to-date and once more it is apparent that great advances can be made with the proper basic science background. The paper by Plentl on the Dynamics of Amniotic Fluid, by Boving on implantation, the one by Vande Wiele on placental steroids are good examples. There is also some excellent teaching in this book, as illustrated by the chapter on blood coagulation in pregnancy.

The only serious objection would concern the last section where one finds 11 papers on relaxin, an interesting substance certainly, but, yet, of obscure biological significance. The fact that this compound actually has reached the market as an agent to either inhibit or accelerate labor has instigated many investigators to carry out clinical trials, all equally unsatisfactory in their final evaluation. The Conference would have been better off without most of these reports.

In summary, one must say that the present selection of papers on reproductive physiology, if nothing else, points to the fact that this field is now being approached as an entity in a most promising way. Interested students and teachers will find this volume worthwhile.

WALTER HERRMANN

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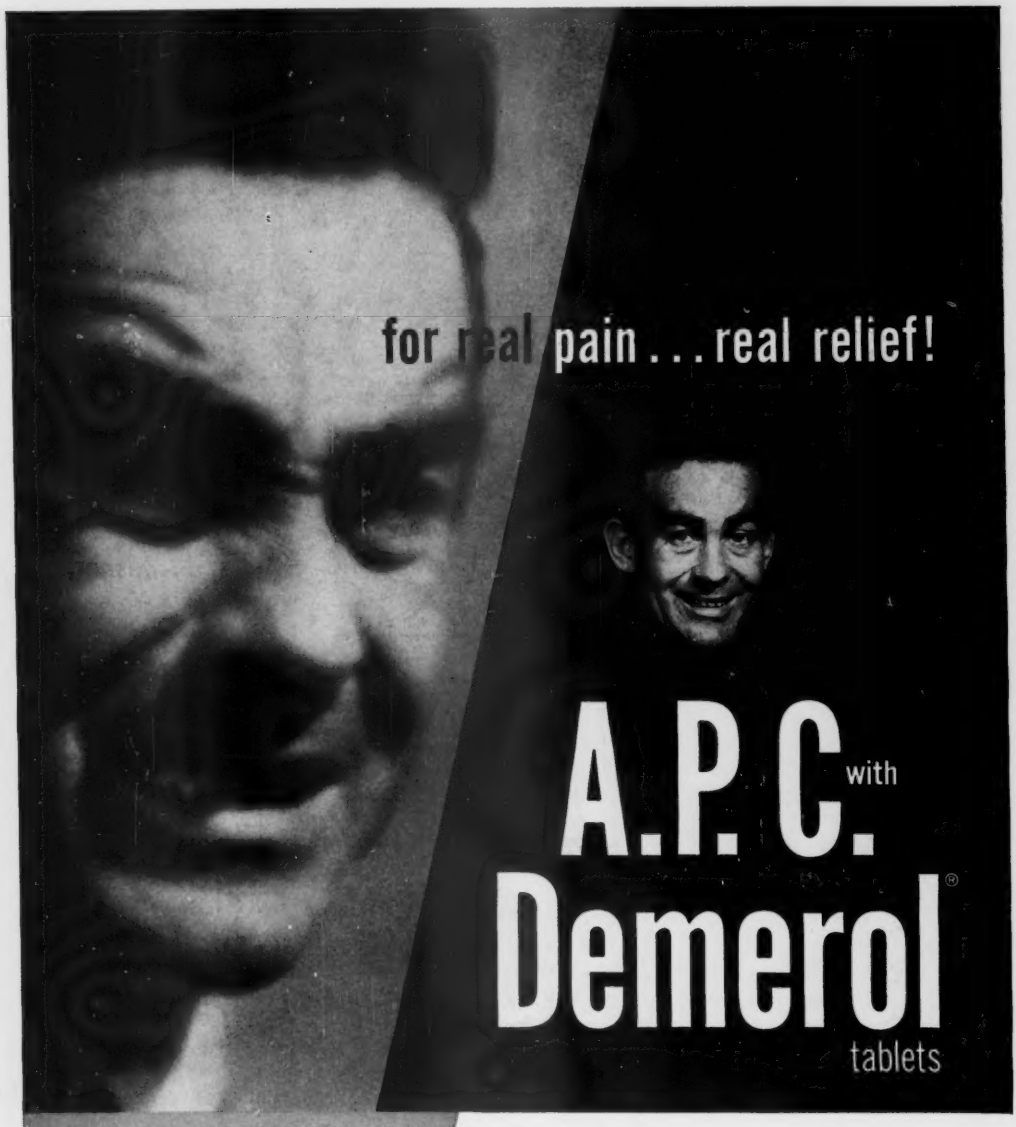

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